Pain Physiology
Pain Pharmacology

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Overview

Pain

Definitions
Physiology
Pharmacology

Chronic Pain

Pathophysiology
Pharmacology

Pain

What is pain

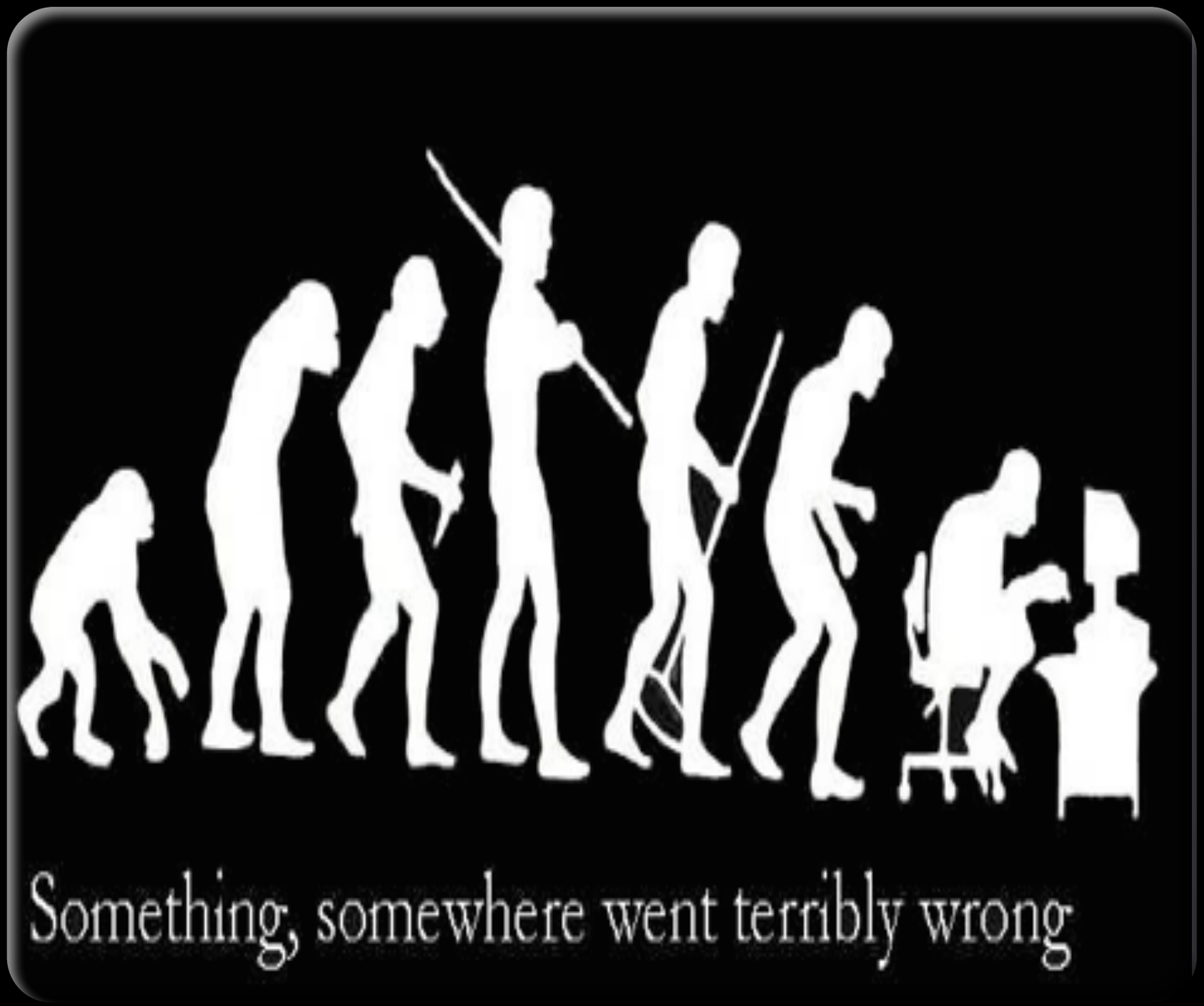
- Pain is an unpleasant sensory and emotional experience associated with or described in terms of tissue injury.

- Has to have an emotional component.
- Has a sensory component

Nociceptive Pain

- Acute inflammatory pain
  - Associated with tissue injury or potential injury
- Nociception is not necessarily pain
  - Has to have an emotional component

Role of nociception



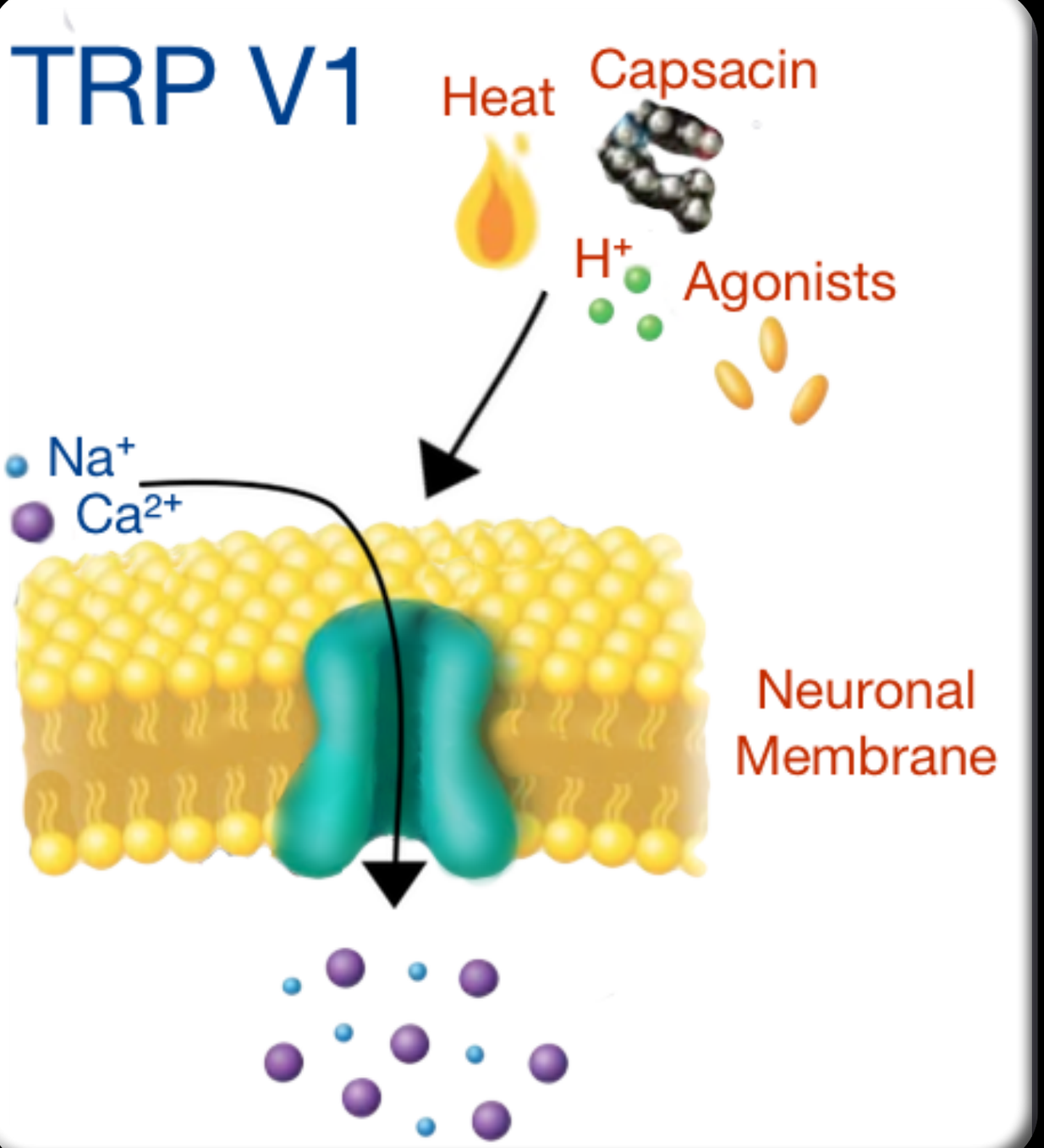
- How did this evolve?
  - Reflexes
  - Nociception
  - Pain
  - Anxiety

Pain Physiology

Pain Pathways

- Descartes (1596-1650) had a good summary:
  - Tissue injury
  - Signal goes to spinal cord
  - Signal travels to brain
  - Pain is sensed
- But it is a little more complex than this

What are the pain sensors?



- Specialized peripheral sensory neurons.
  - Designed to detect tissue injury
  - High threshold sensors
    - Temperature > 40 Celcius
    - Temperature < 15 Celcius
    - Pressure
    - Chemical sensors
  - Narrow dynamic range

Pain Sensors

Heat

TRPV1, V2, V3
TREK -1

Acid

TRPV1
ASIC, DRASIC

Mechanical

MDEG, TREK1
DRASIG

Cold

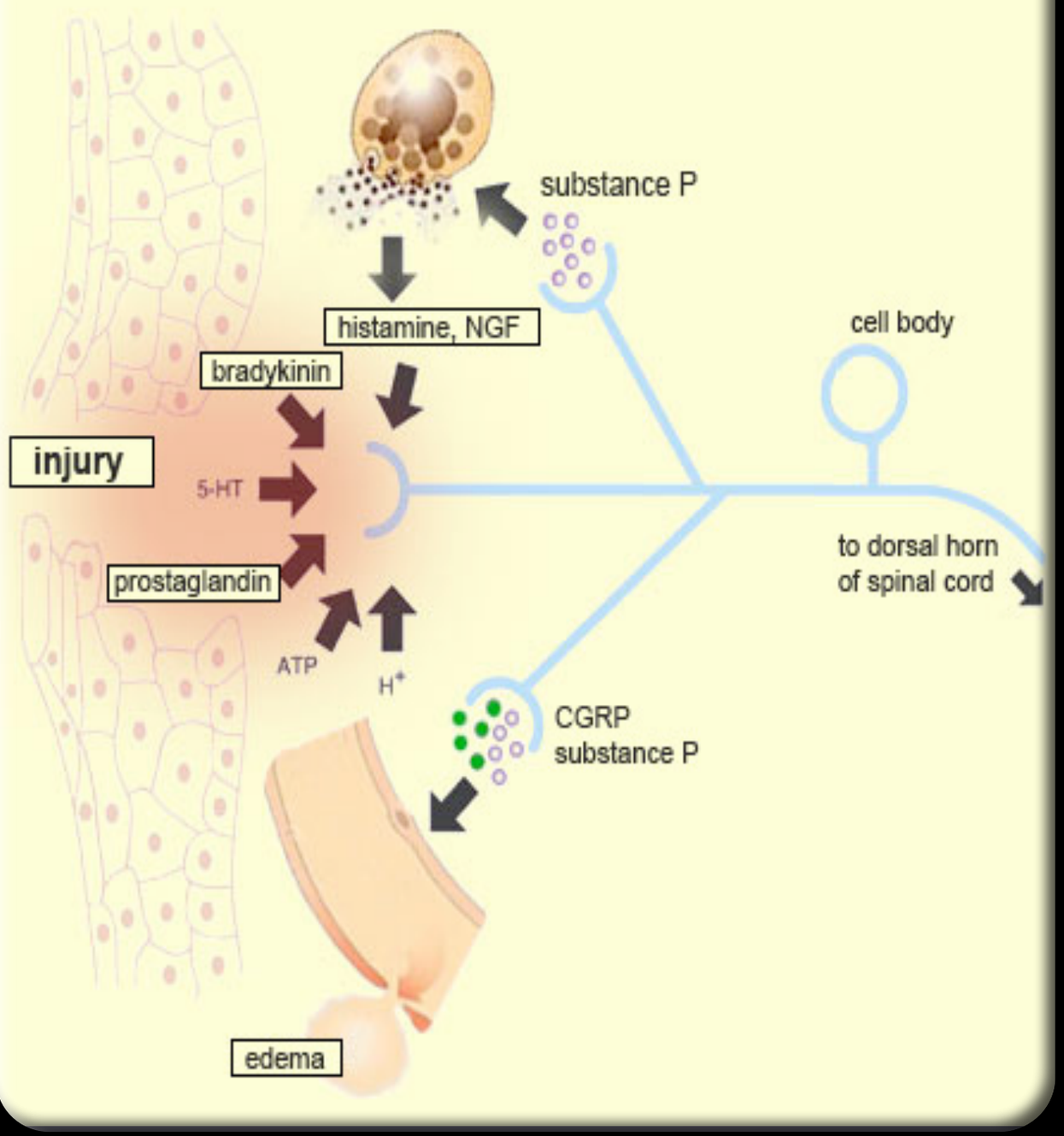
TRPV8

DRG

Sensitisation

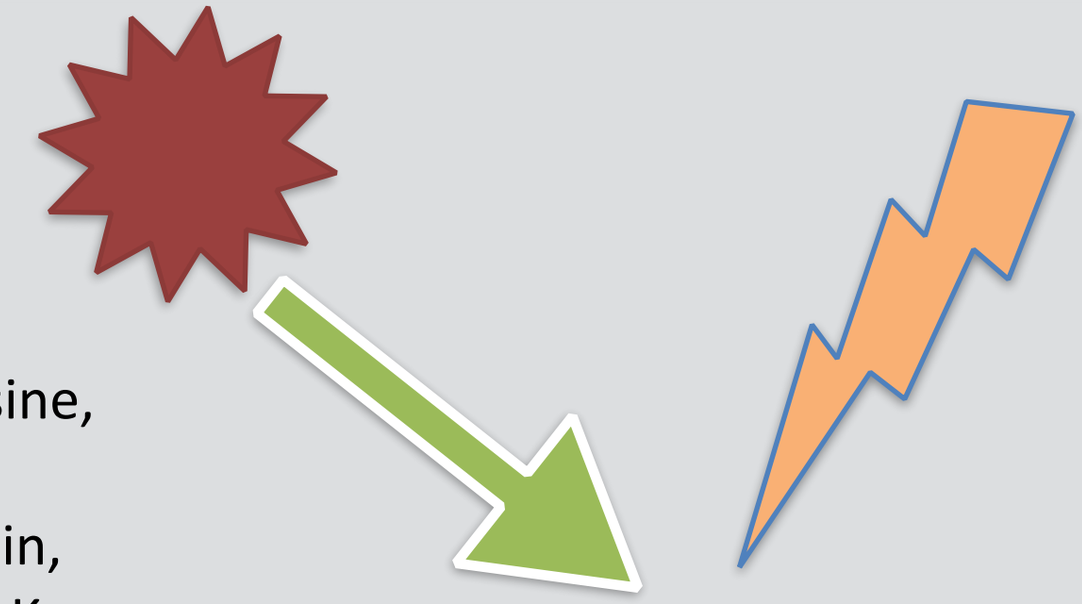
- Hyperalgesia
  - An increase in pain for a painful stimulus
- Allodynia
  - A painful sensation in response to a non painful stimulus

Peripheral Sensitisation



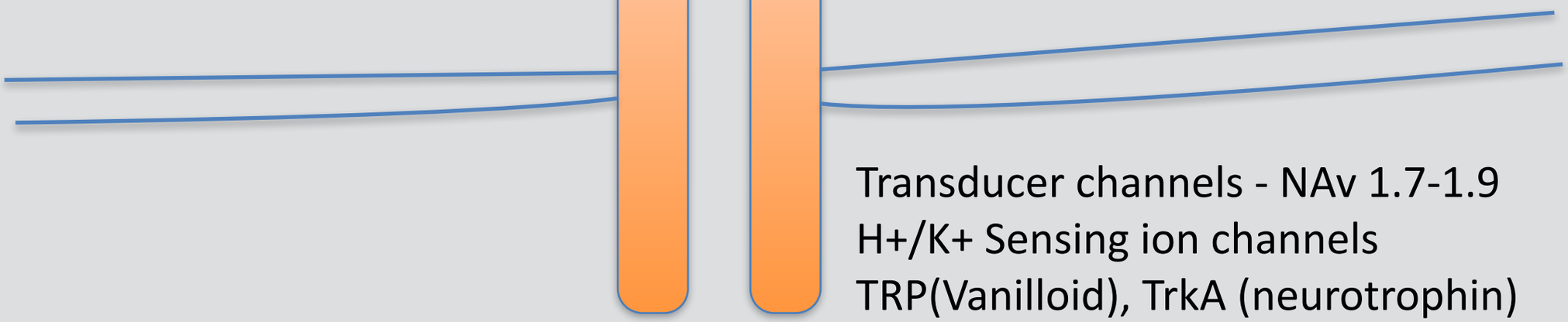
- Due to inflammatory mediators
  - Prostaglandins
  - Bradykinin
  - Histamine
  - Serotonin
  - ATP
  - Acid (H^+)

Nociception



AcH, ATP, PGE2,
Glutamate, Adenosine,
Bradykinin
Histamine, Serotonin,
Noradrenaline, H+, K+
Cytokines (IL1, IL6, TNF)

Mechanical, thermal or
other stimulus



Transducer channels - NAv 1.7-1.9
H+/K+ Sensing ion channels
TRP(Vanilloid), TrkA (neurotrophin)

Conduction of signals

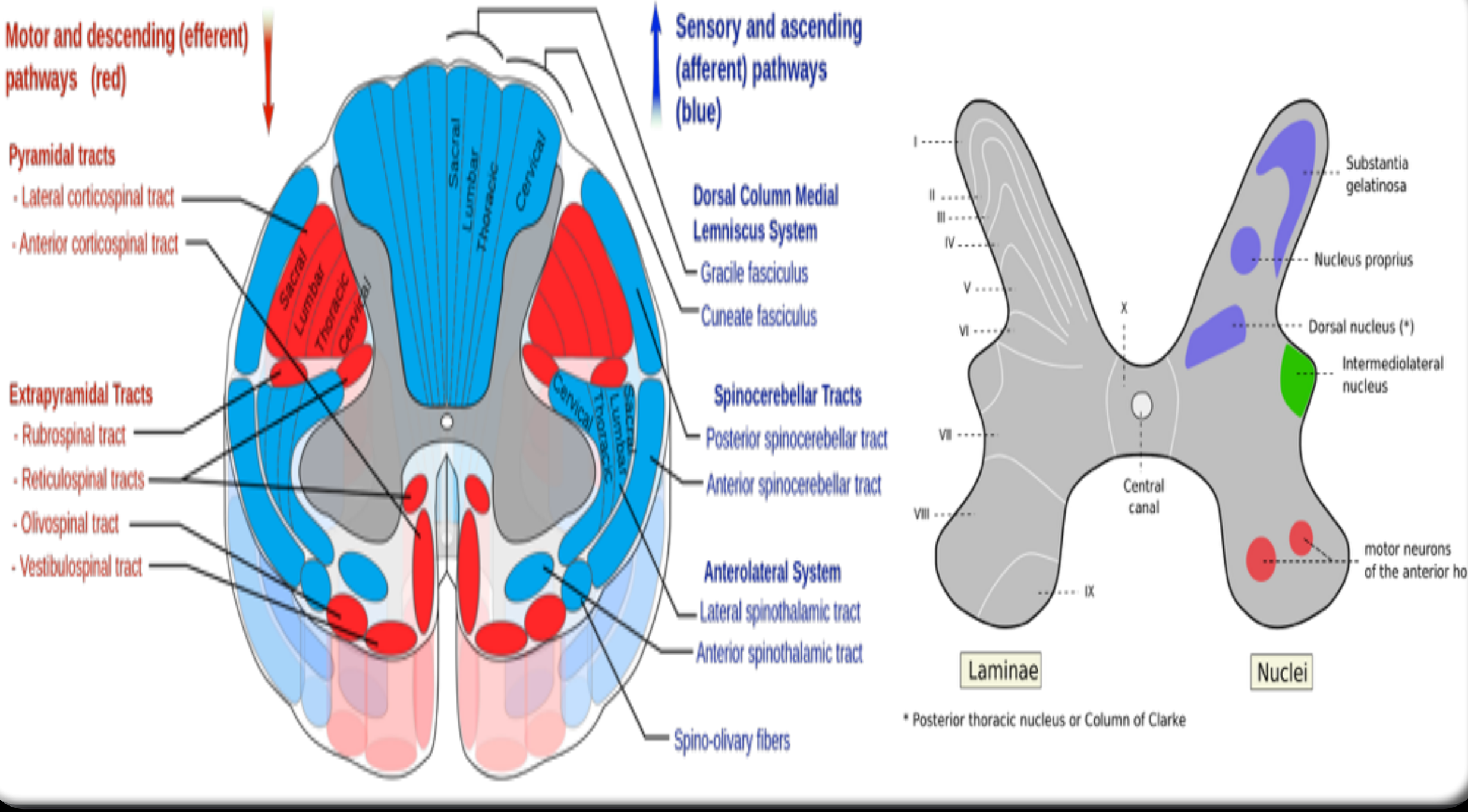
Fibres	Aδ	C	Aβ
Threshold	Low & High	High	Pathological
Stimulii	Thermal Mechanical	Thermal Mechanical Chemical	Mechanical Light Touch
Diameter	2-5 μm	0.5-2 μm	5-10 μm
Conduction Velocity	10-30 m/s	0.5-2 m/s	30-60 m/s

Nociception ≠ Pain

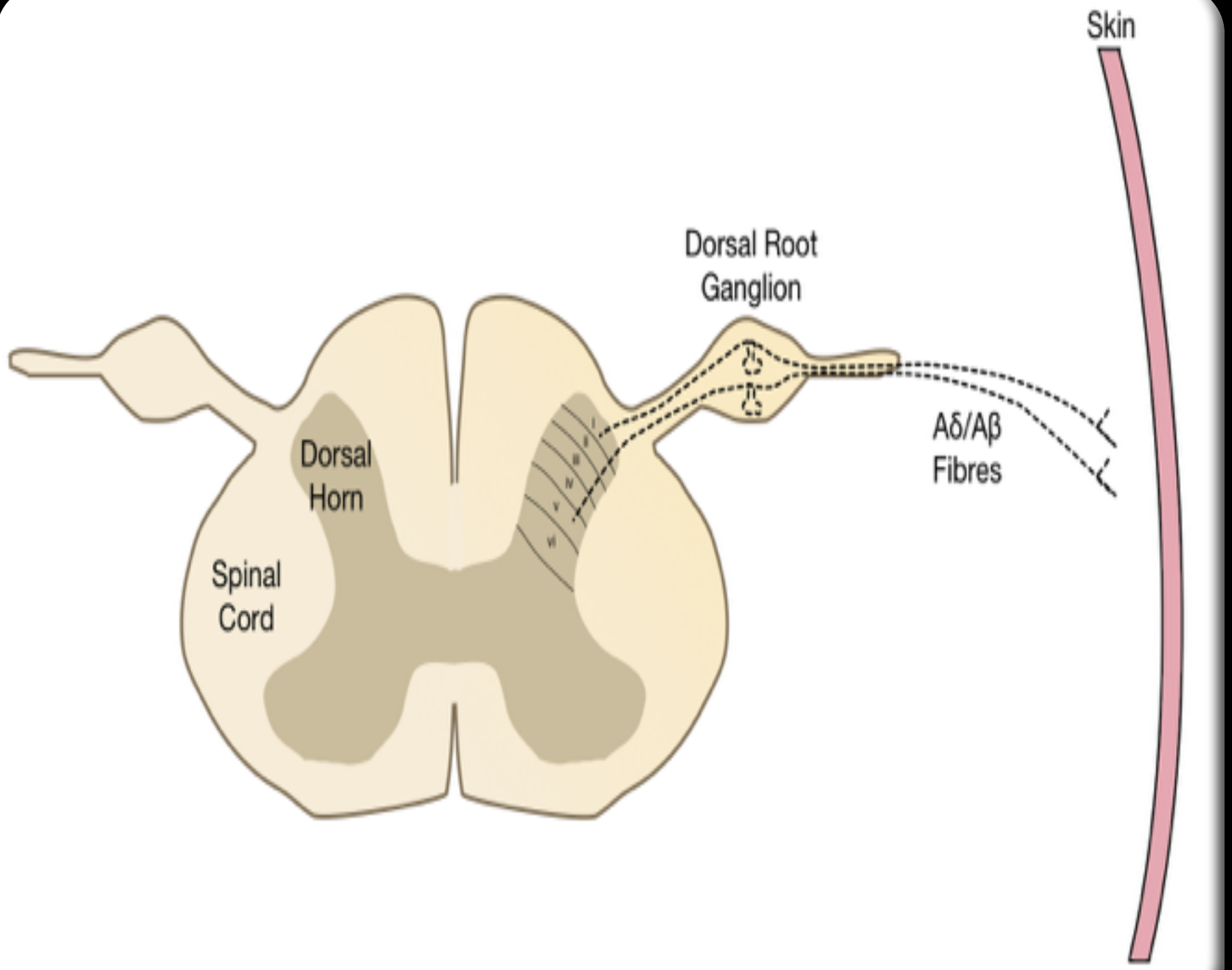
Aδ - Fast Pain

C - Slow pain

Spinal pathways.
This all looks rather complex



Aδ Fibres



Sense:

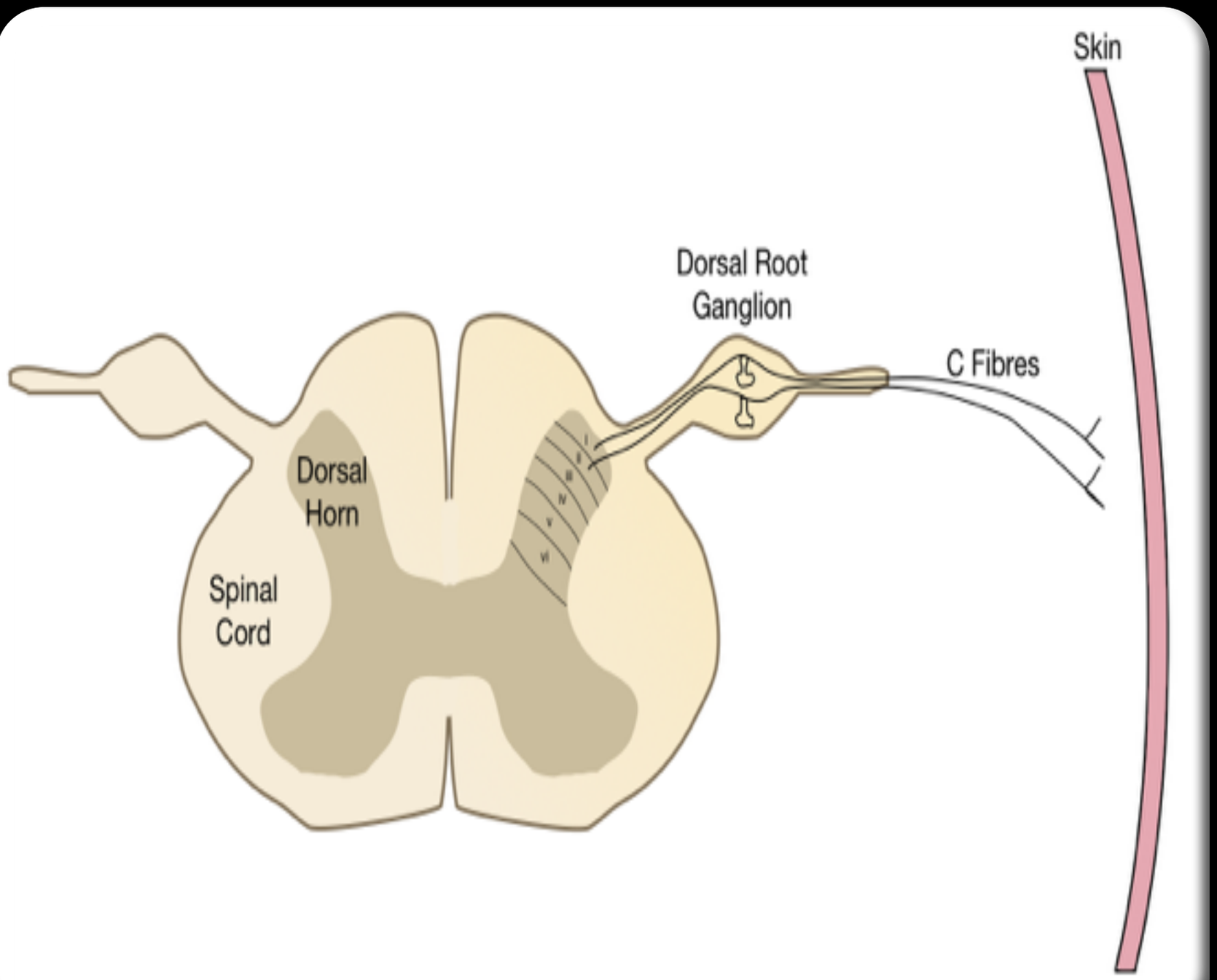
Heat

Pressure

Noxious Cold

Fast Conducting

C Fibres



Sense:

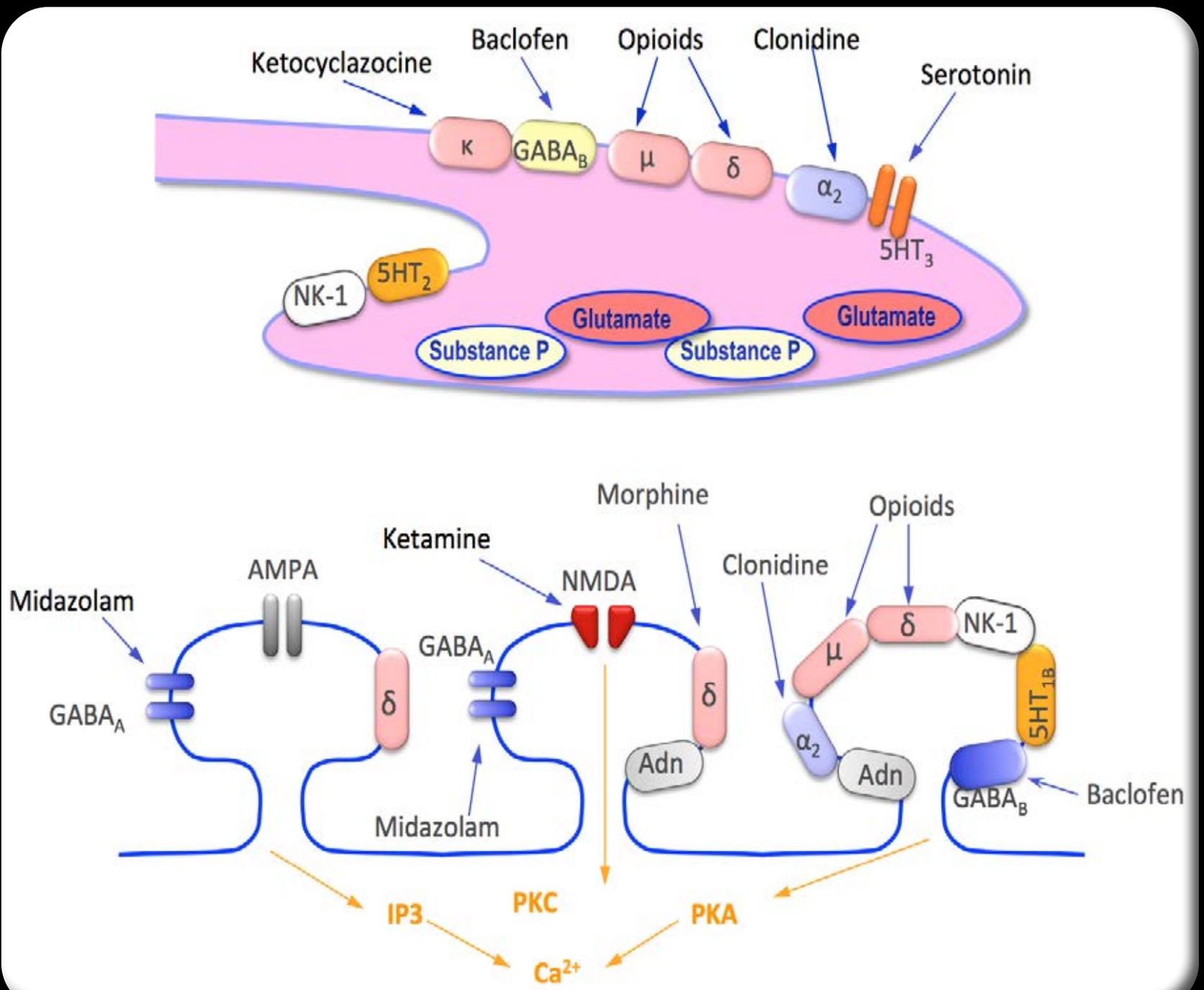
Thermal (hot/cold)

Mechanical

Chemical

Slow conducting

What happens in the lamina?



Transmission across synapse

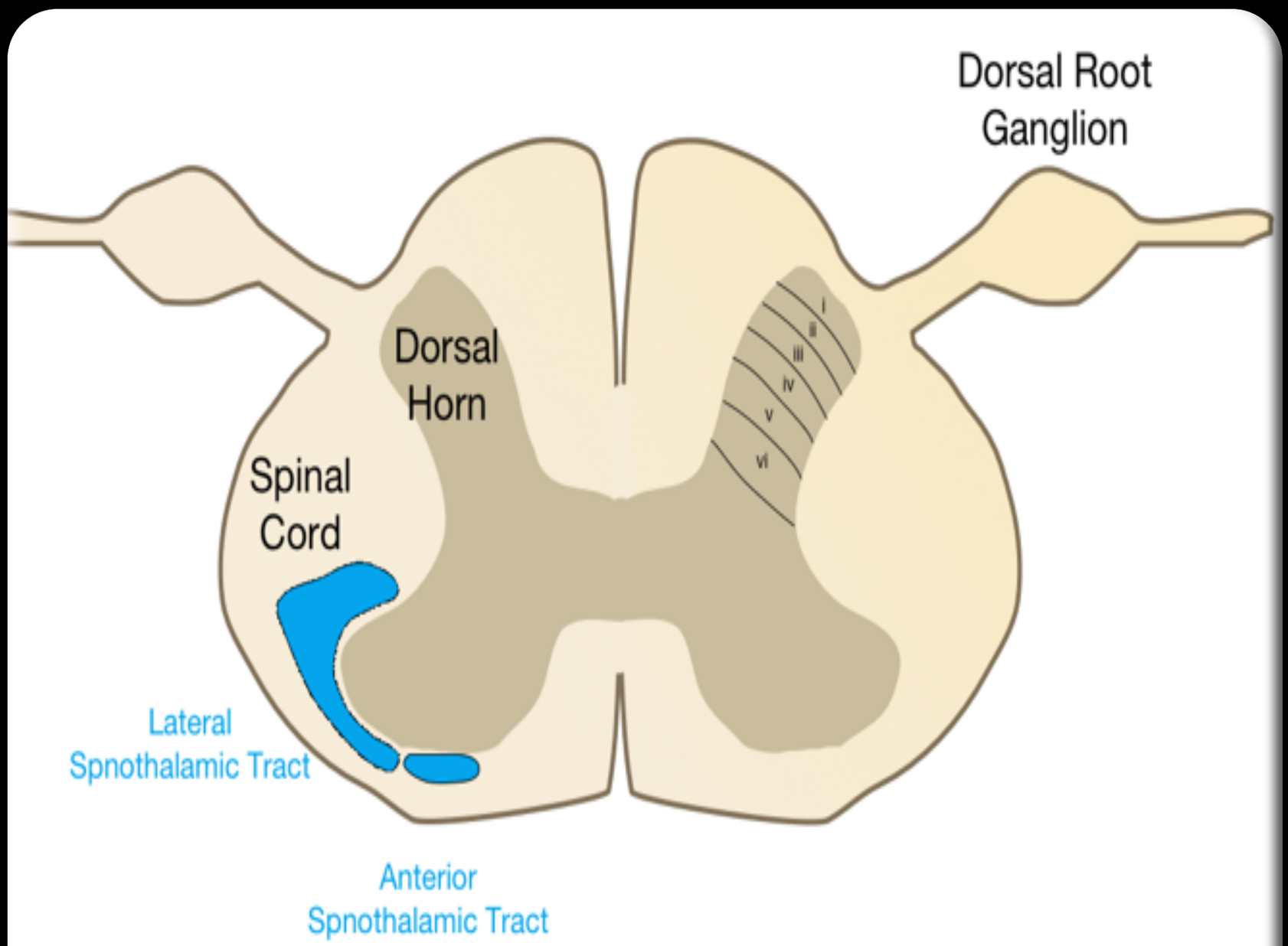
1st order neurons

-> Transmitter

2nd order neurons

The most important transmitter is glutamate

Transmission to Brain



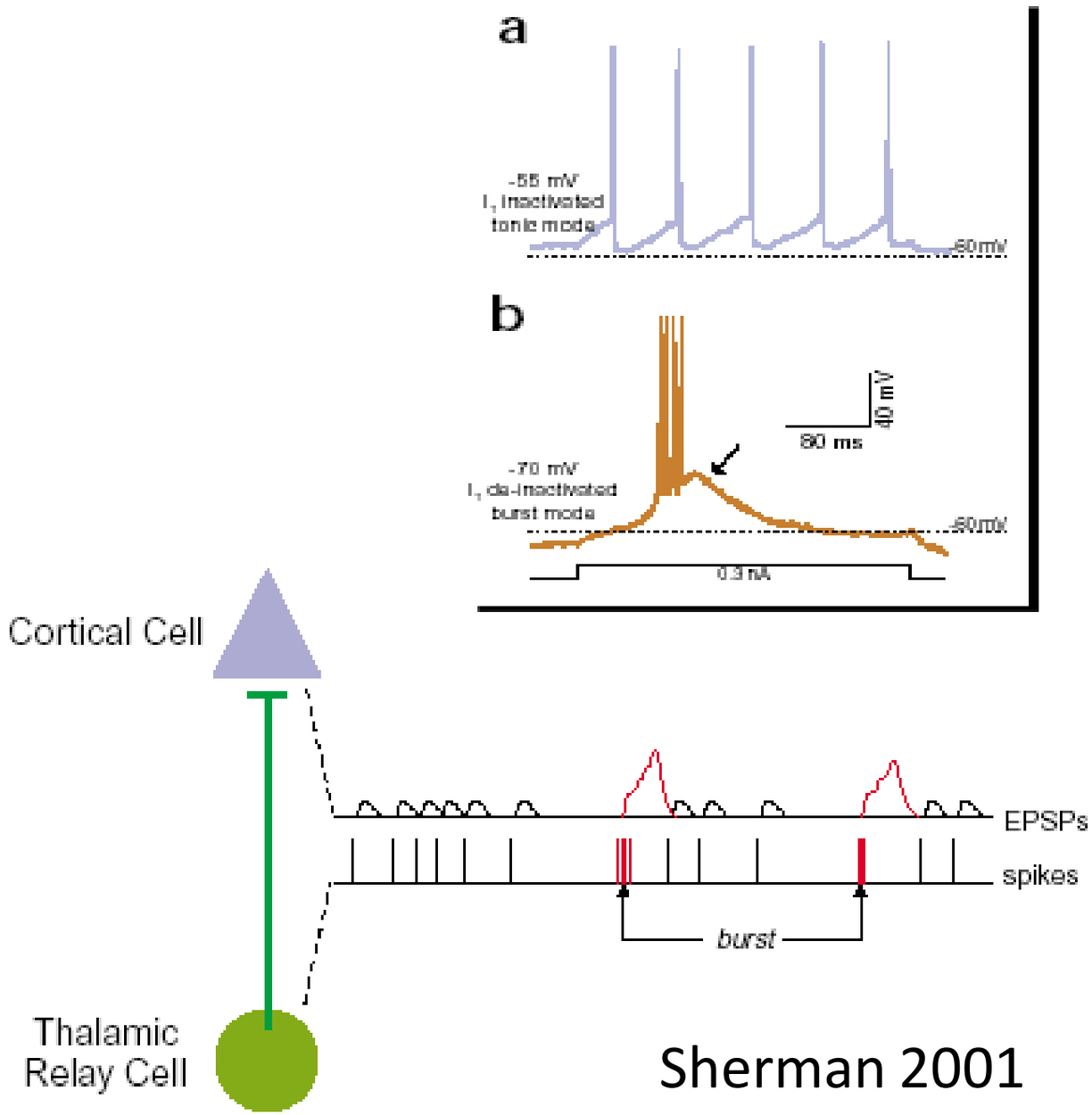
Second order neurons

Signals cross over

Lateral Spinothalamic tract

Anterior Spinothalamic tract

Signalling of pain



Sherman 2001

Burst mode is signal detector

Tonic is feature detector

Sherman 2001

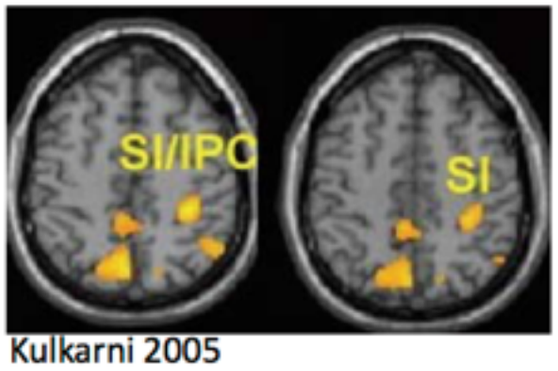
Cooper 2006

Burst has a non-linear response

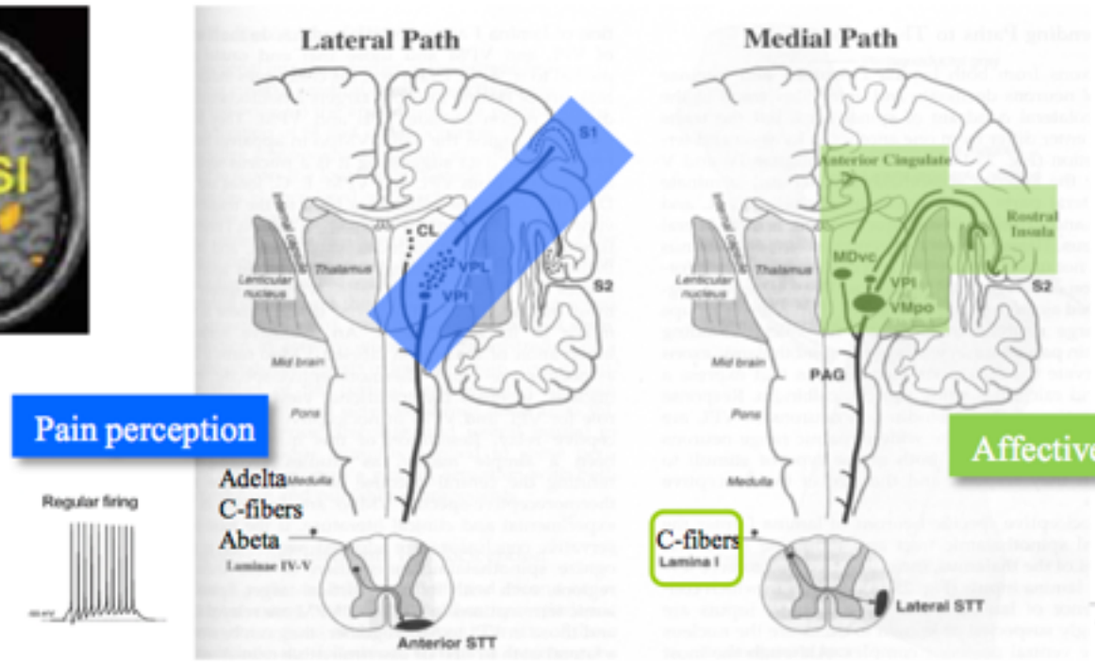
Lisman 1997

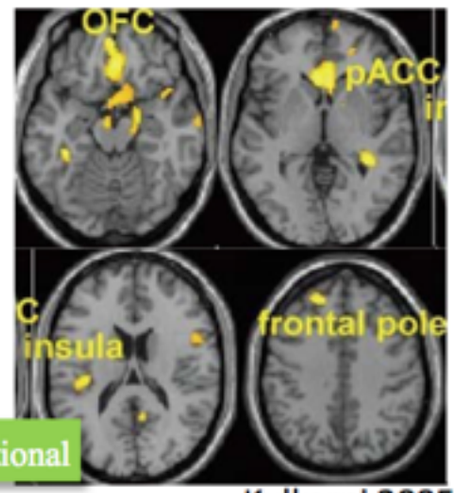
Sherman 2001

Two Pain Pathways



Kulkarni 2005

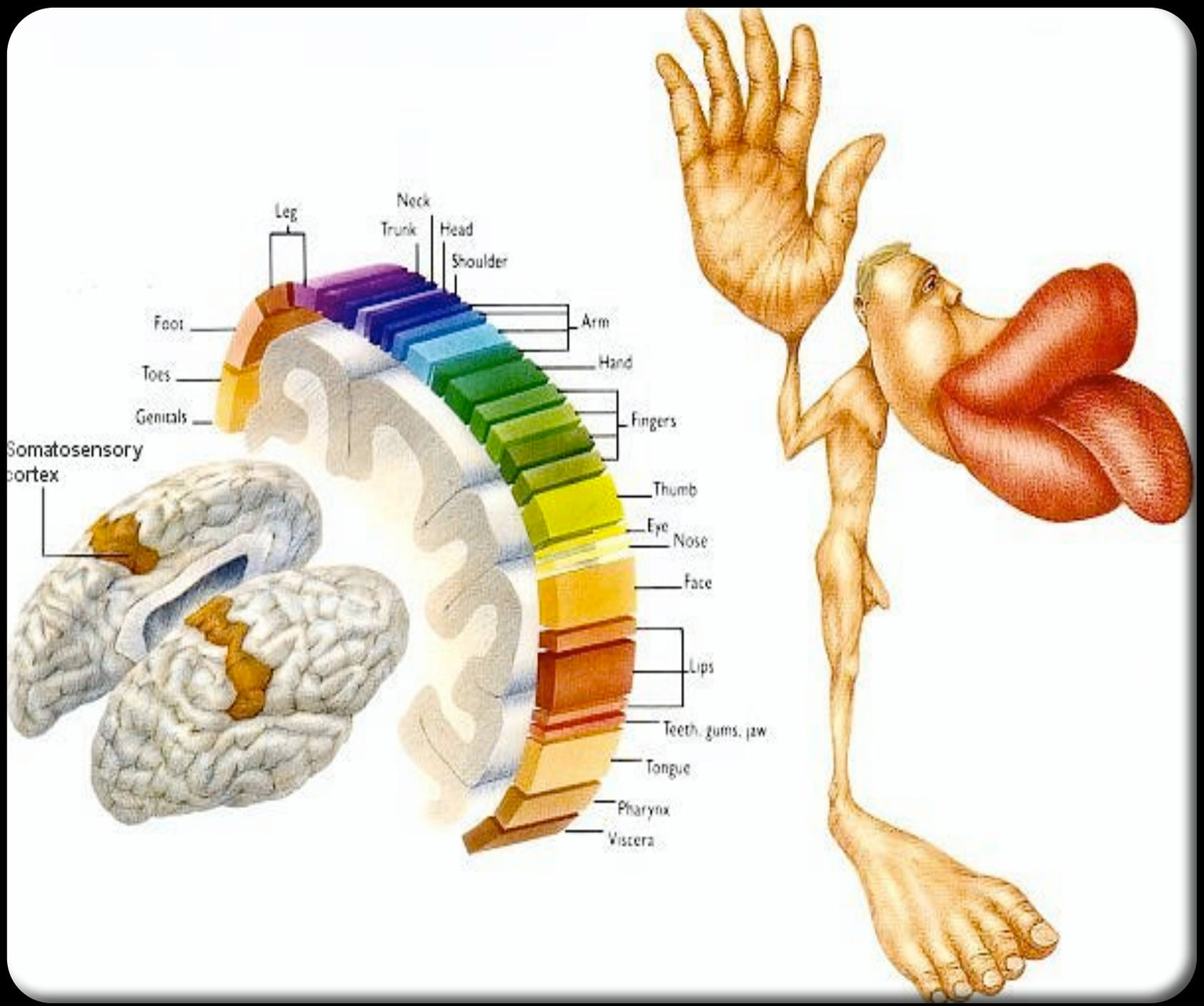




Kulkarni 2005

Lateral System (Pain Perception)	Medial System (Affective)
WDR neurons	Nociceptive neurons
Firing in tonic mode	Fire in burst
Lamina I, V-VI	Lamina I

Somatosensory Cortex



Sensory Homonculus

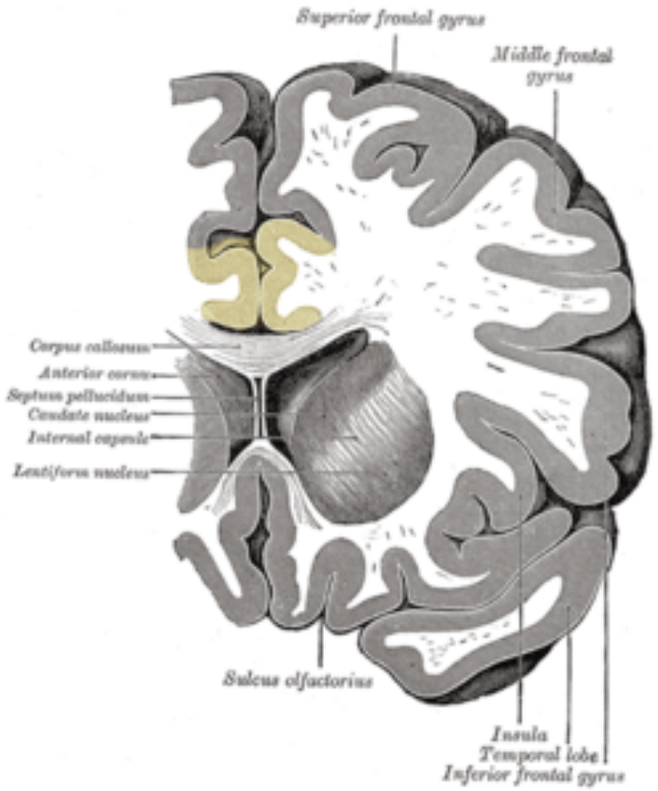
S1

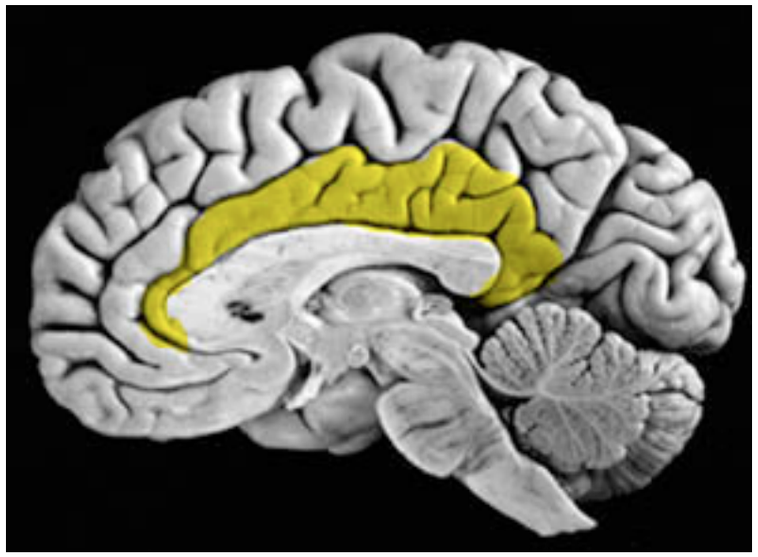
S2

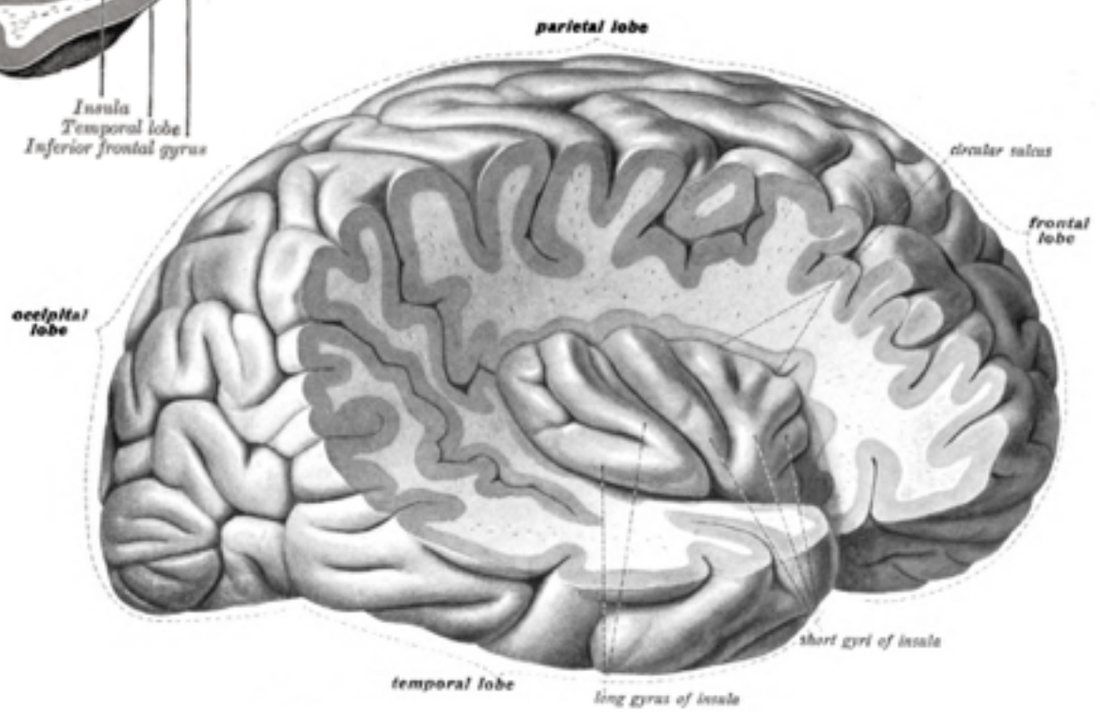
Parietal Lobe

Post central gyrus

Emotional Response





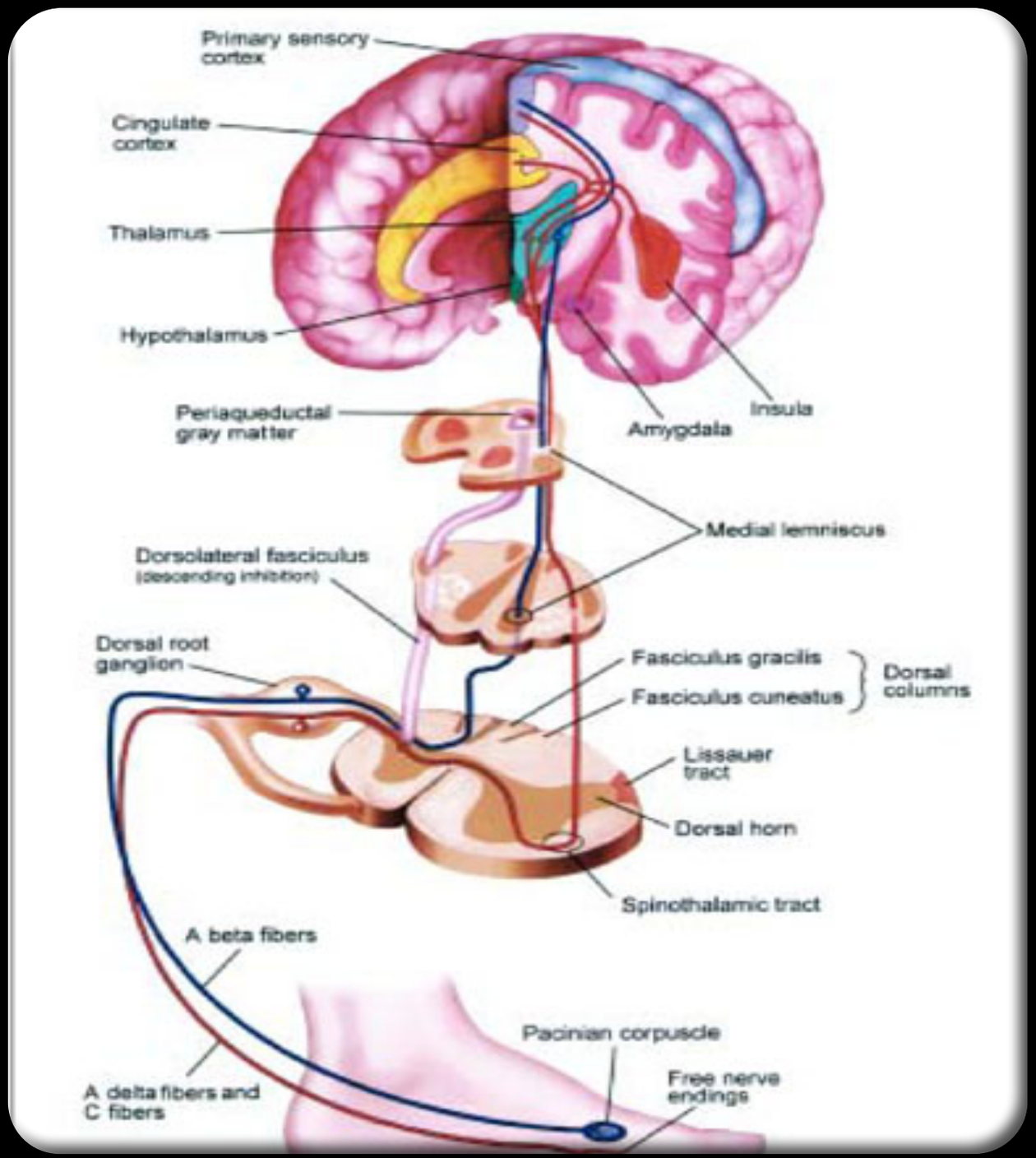


- Anterior Cingulate Gyrus
- Insula

Descending Noxious Inhibitory Controls

- Neurons in the dorsal horn are wide dynamic range
  - Can be inhibited by descending pathways
- Reduced DNIC is associated with various pain conditions

DNIC
Dampens the signals



- Periaquaductal Grey Matter regulates this downward signalling
  - Dorsolateral Furniculus
- Mediators include
  - Noradrenaline
  - Serotonin

Placebo

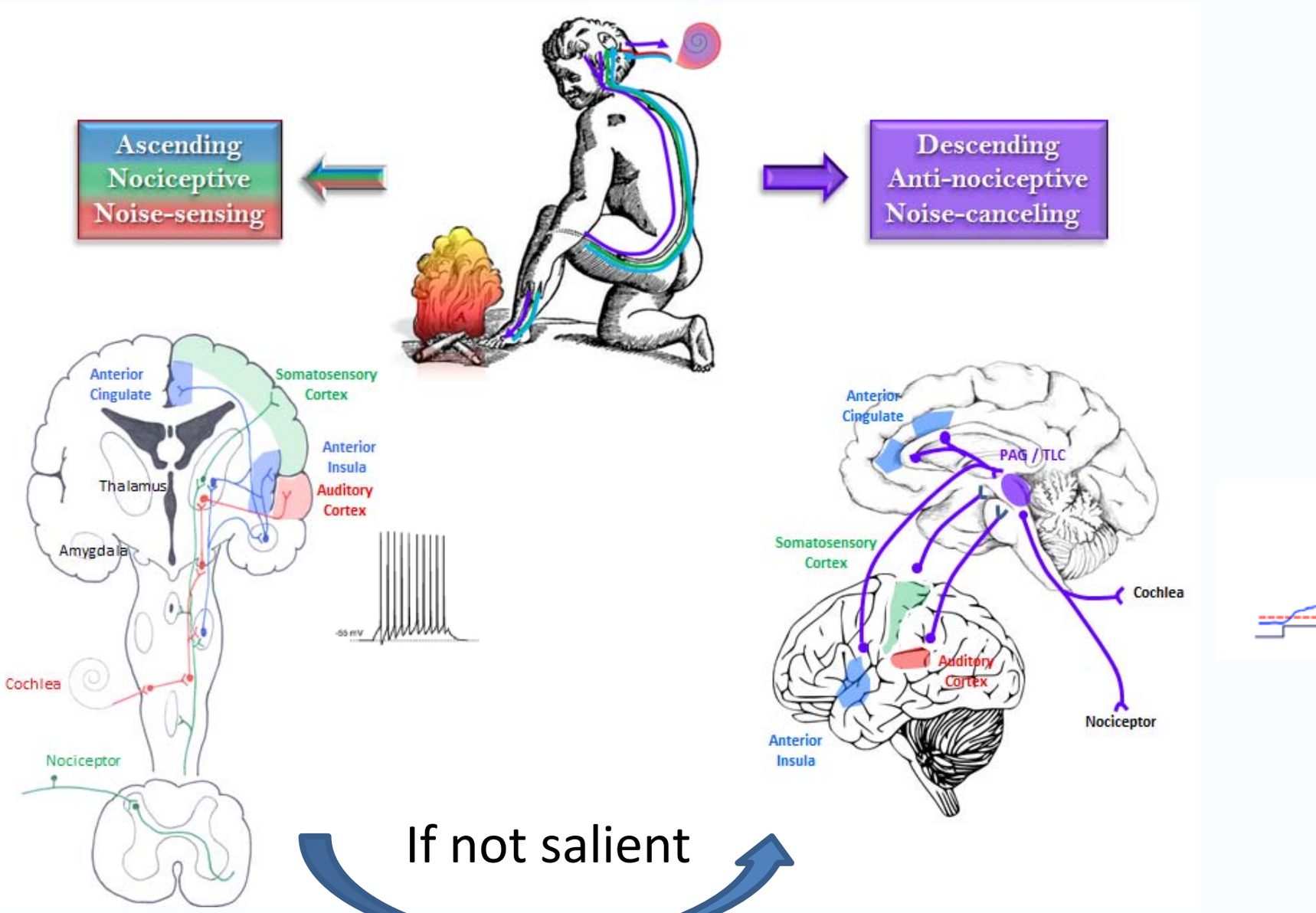
Placebos and Pain

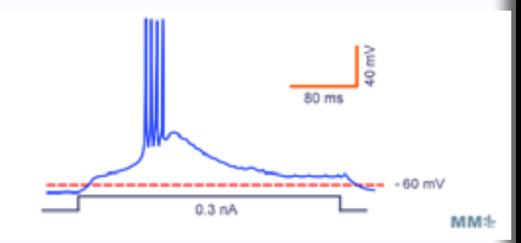
- In pain, the placebo effect isn't a placebo
  - There is a biological basis for this
  - If the pain gets better, its a treatment
  - Makes treatments harder to assess
- Probably uses same mechanisms as acupuncture, hypnotherapy

Nocebo

- From latin “I shall harm”
- An inert substance that creates harmful effects
- Has significance in pain medicine
  - People withdraw from placebo arm of drug trials

Overview of pain pathways





Pain Pharmacology

Acute Pain Management

- Nociceptive pain
  - Emergency departments
  - Acute post surgical pain
  - General practice
- Usually traumatic

Stepped approach

- Paracetamol
- Non steroidal anti inflammatory drugs
- Opiates
  - Tramadol, Tapendatol, Buphrenorphine
  - Hydromorphone, Morphine, Fentanyl, Oxycodone, Pethidine
- Adjuncts

Paracetamol

- Effective, safe (< 4g/day), oral or IV
  - Ceiling effect limits benefit for severe pain
  - Analgesic and antipyretic
- Reduce dose with liver dysfunction

NSAID's and Coxib's

- NSAID's
  - Aspirin
  - Diclofenac, Naproxen, Ibuprofen, Indomethacin, Meloxicam.
- Coxib's
  - Celecoxib, Parecoxib

NSAID's

- Inhibit cyclo-oxygenase (COX-1 & COX-2)
  - Reduced synthesis of prostaglandins
- COX-1 inhibition causes many side effects
  - GI upset
  - Asthma

COX-2 inhibition

- Celecoxib (orally), Parecoxib (intravenous)
  - Analgesia, antipyretic effects
  - Renal impairment (?)
  - Myocardial infarction (Rofecoxib/“Vioxx”)

Tramadol

- Atypical opiate
  - 40% opiate
  - 40% noradernergic reuptake inhibition
  - 20% serotonergic reuptake inhibition
- Very good safety profile
- Side effects
  - Nausea

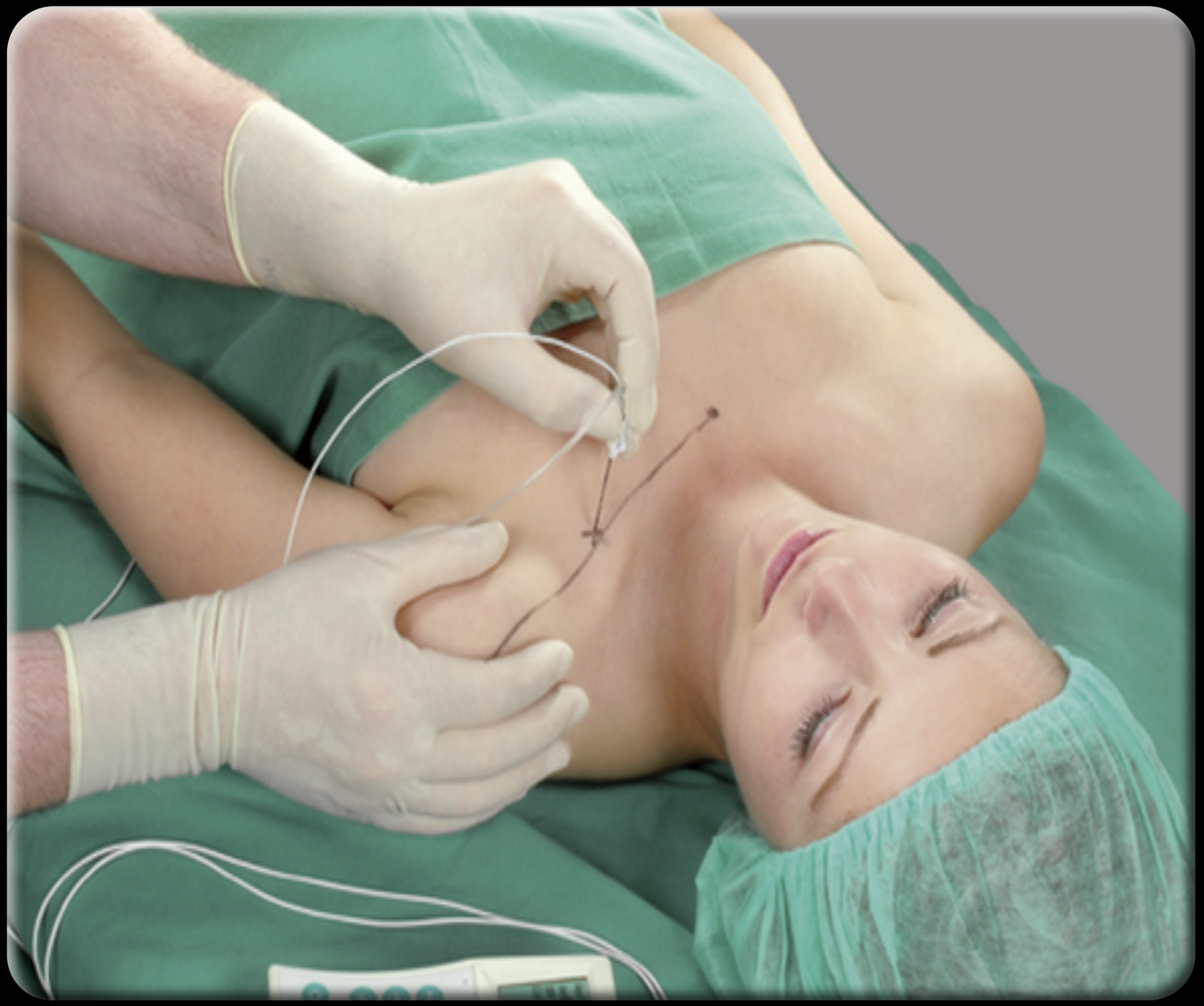
Opiates

- Very useful in acute pain
  - Best reserved for severe pain
  - Oral or parenteral (IV)
- Mechanism
- Side effects
  - Respiratory depression, constipation, nausea

Nerve blockade

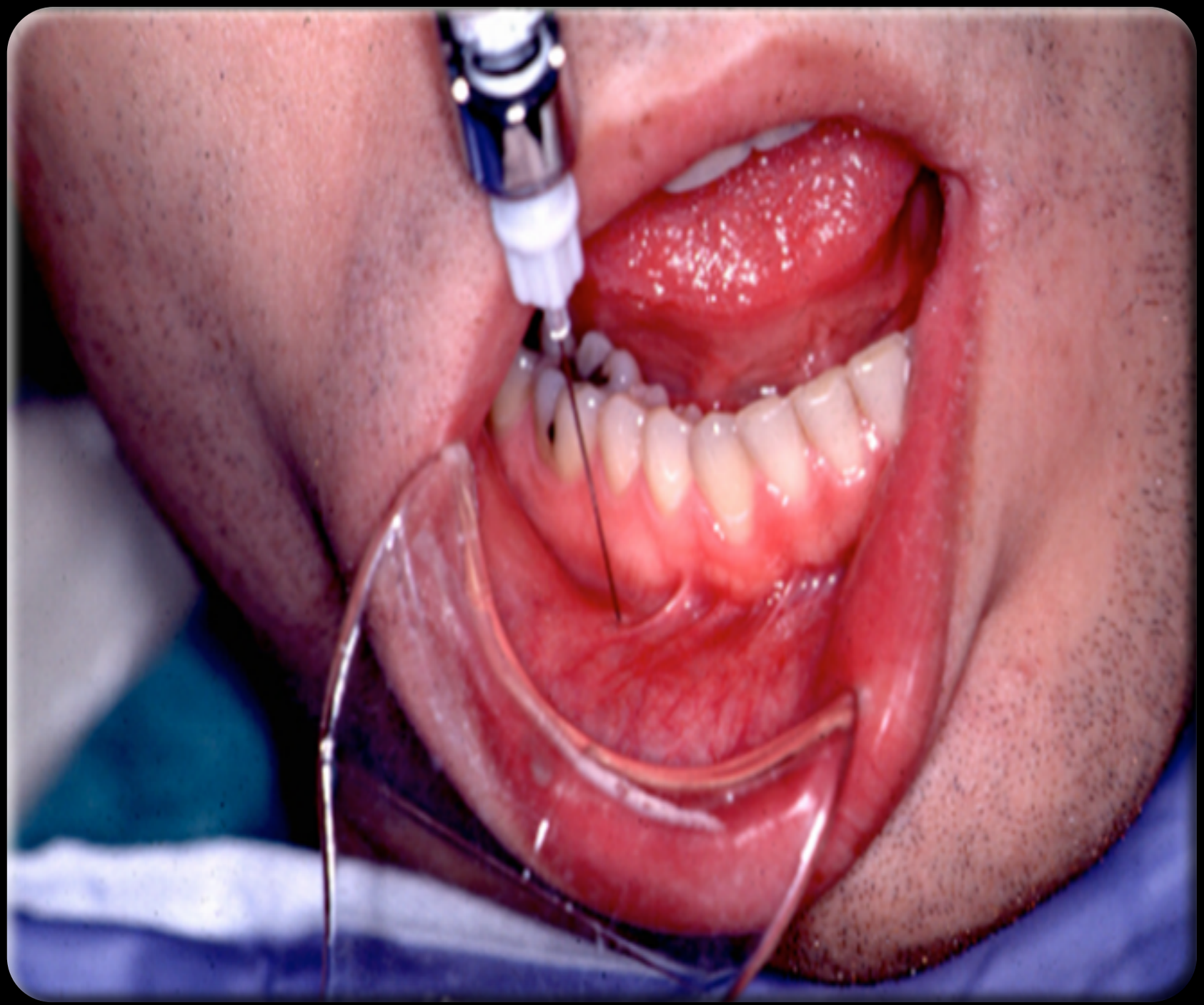
- Central Neuraxial
  - Epidural
  - Spinal

Nerve Blockade



- Major nerve blocks
  - Sciatic
  - Femoral
- Plexus
  - Brachial
  - Lumbar

Local Infiltration



- Direct to tissues
- Peripheral nerve blocks

Chronic Pain

Neuropathic Pain

Sensitisation

Hyperalgesia

Allodynia

Hyperpathia

Neuropathy

- An injury or disease of the neurone
  - Implies loss of function (usually motor)

Neuropathic Pain

- A disease of the somatosensory system that leads to pain perception
  - Peripheral nerve injury
  - Central pain states

Hyperalgesia

- Increased sensitivity to pain
  - Painful stimuli hurt more
  - Is part of sensitisation
- Can affect different modalities
  - Cold/ Hot/ Pinprick

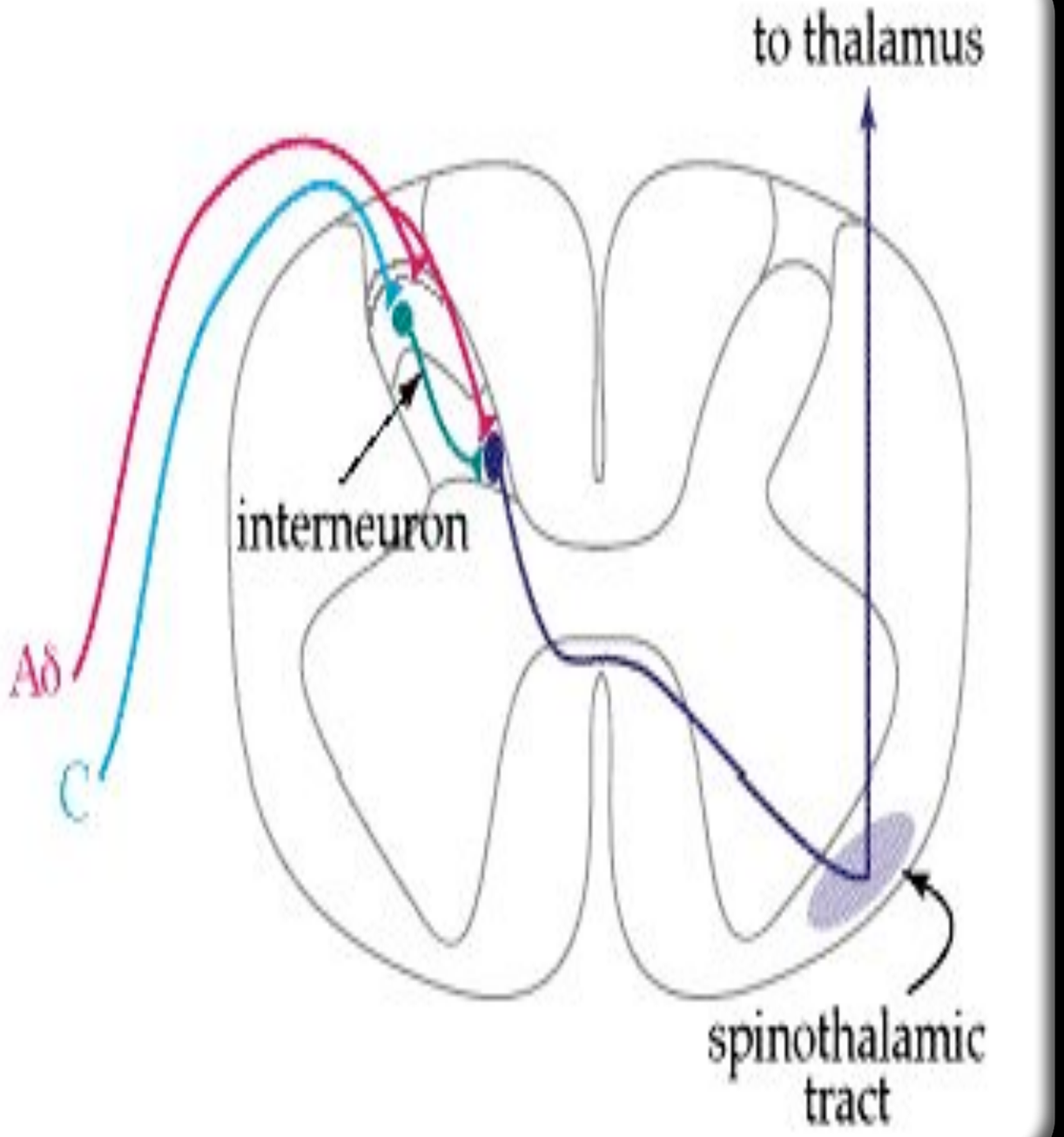
Allodynia

- Non painful stimuli cause pain
  - Due to sensitisation
- Can be felt in multiple modalities
  - Hot/ Cold/ Light touch/ pinprick

Hyperpathia

- Summative response to stimuli causing increasing pain.

Central Sensitisation



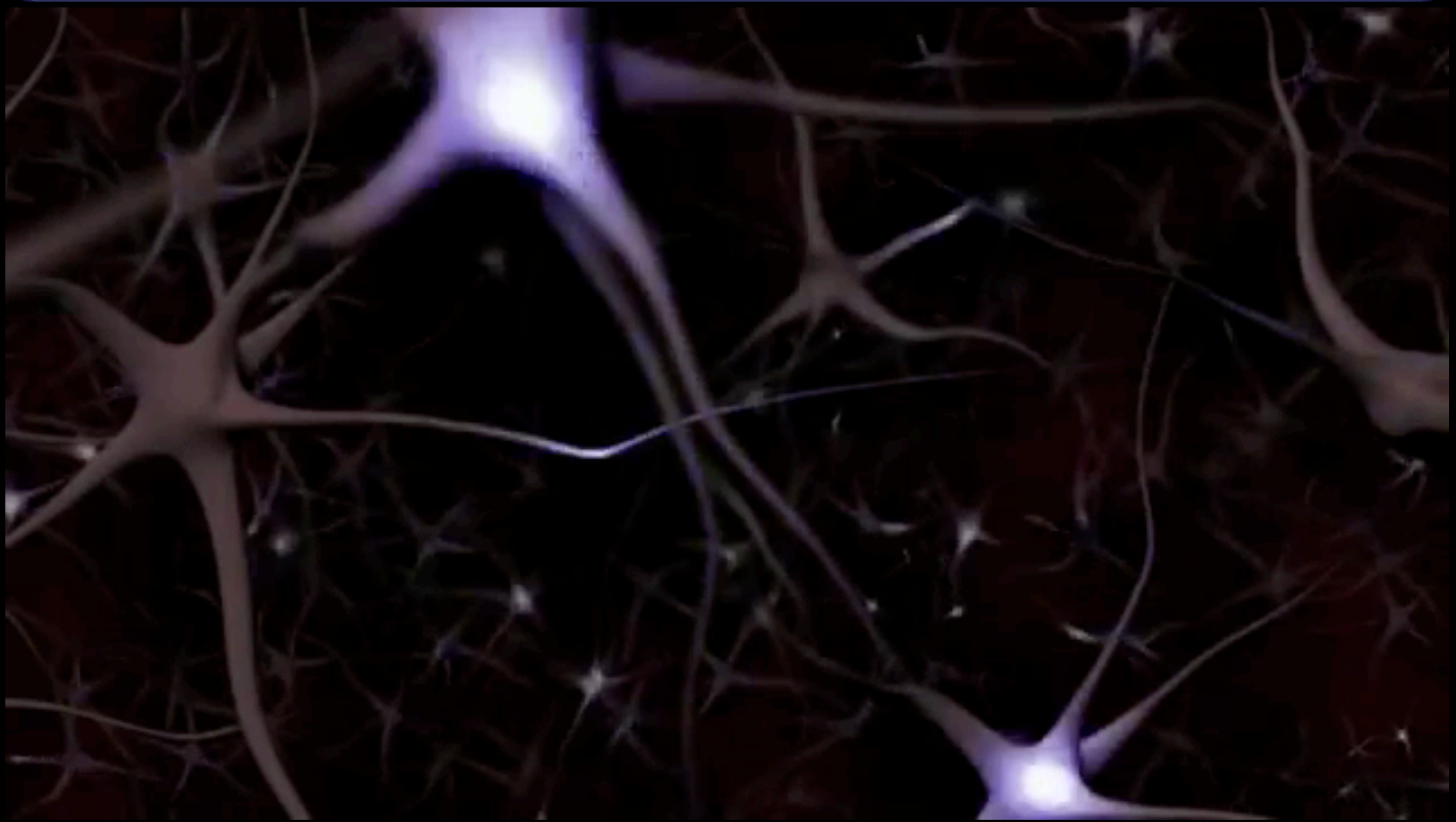
- Amplification of pain perception despite normal peripheral nociception.
- Central sensitisation is associated with dorsal horn in spinal cord.
- Glutamate is a major mediator of this

Chronic Pain & Glia

Glia Overview

- What are Glia?
  - Astrocytes
  - Microglia
- How do glia influence neurons?

Neuronal Activity



Neurons don’t float

- 10% of cells in the brain are neuronal
- 90% are glia.
  - Astrocytes
  - Microglia
  - Satellite Glial Cells
  - Others (Oligodendrocytes, Ependymal cells)
- Glia aren’t just scaffolding

Immunology and the brain

- Brain modifies the immune system
  - Direct connections to immune organs (spleen)
  - Hormonal regulation - eg via cortisol
- Immune system modifies the brain
  - Microglia & Astrocytes

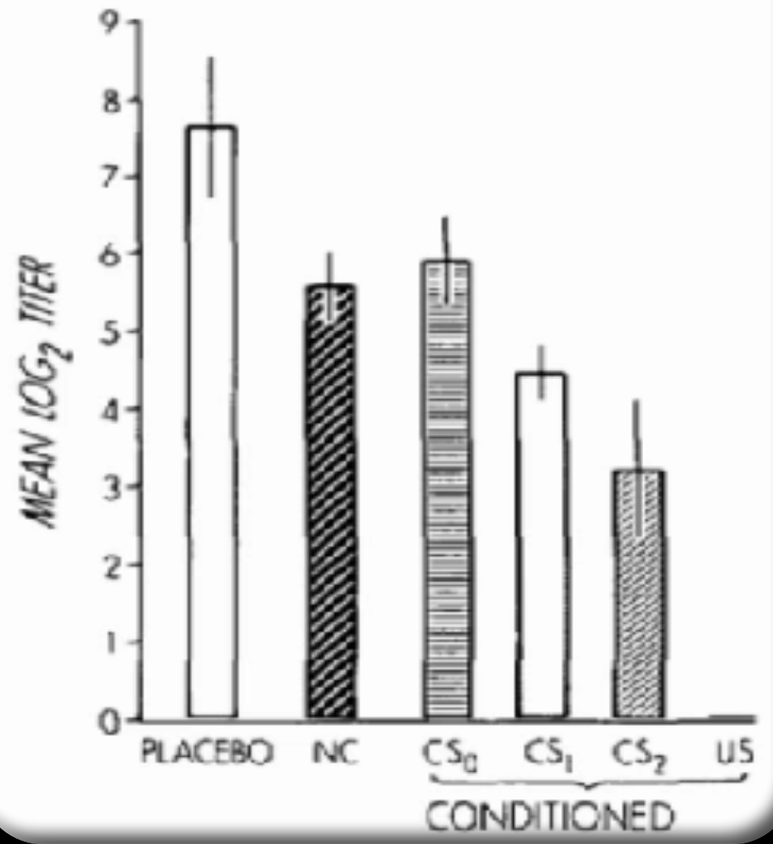
Brain to immune connection

- Psycho-immunology (Solomon 1960's)
  - Suggested that psychiatric disorders influenced the immune system
- Shunned by scientific community

Taste conditioned immunosuppression

TABLE 1. Experimental Treatments

Group	Day 0 Drnk. Soln.	Day 0 Inj.	Subgroup	N	Day 3 Drnk. Soln.	Day 3 Inj.	Day 6 Drnk. Soln.	Day 6 Inj.
Conditioned								
(N = 67)	Saach.	CY	CS_1	11	Sacch	Sal	H_2O	—
				9	H_2O	—	Sacch	Sal
			CS_0	10	H_2O	Sal	H_2O	—
				9	H_2O	—	H_2O	Sal
			US	10	H_2O	CY	H_2O	—
				9	H_2O	—	H_2O	CY
			CS_2	9	Sacch	Sal	Saach	—
Nonconditioned								
(N = 19)	H_2O	CY	NC	10	Sacch	Sal	H_2O	—
				9	H_2O	—	Sacch	Sal
Placebo								
(N = 10)	H_2O	Placebo	P	10	H_2O	—	H_2O	—



- 1975
  - Ader et al

Implications of brain to immune signalling

- If your brain controls your immune response
  - Placebo effects?
  - Disease progression (eg cancers)
  - Comorbidities
    - Diseases (eg depression)
    - Drug therapies (eg opiates)

Central Immune Signalling

- Neuroinflammation is an extreme example
  - Trauma
  - Injury
  - MS
  - Stroke
  - Tumours

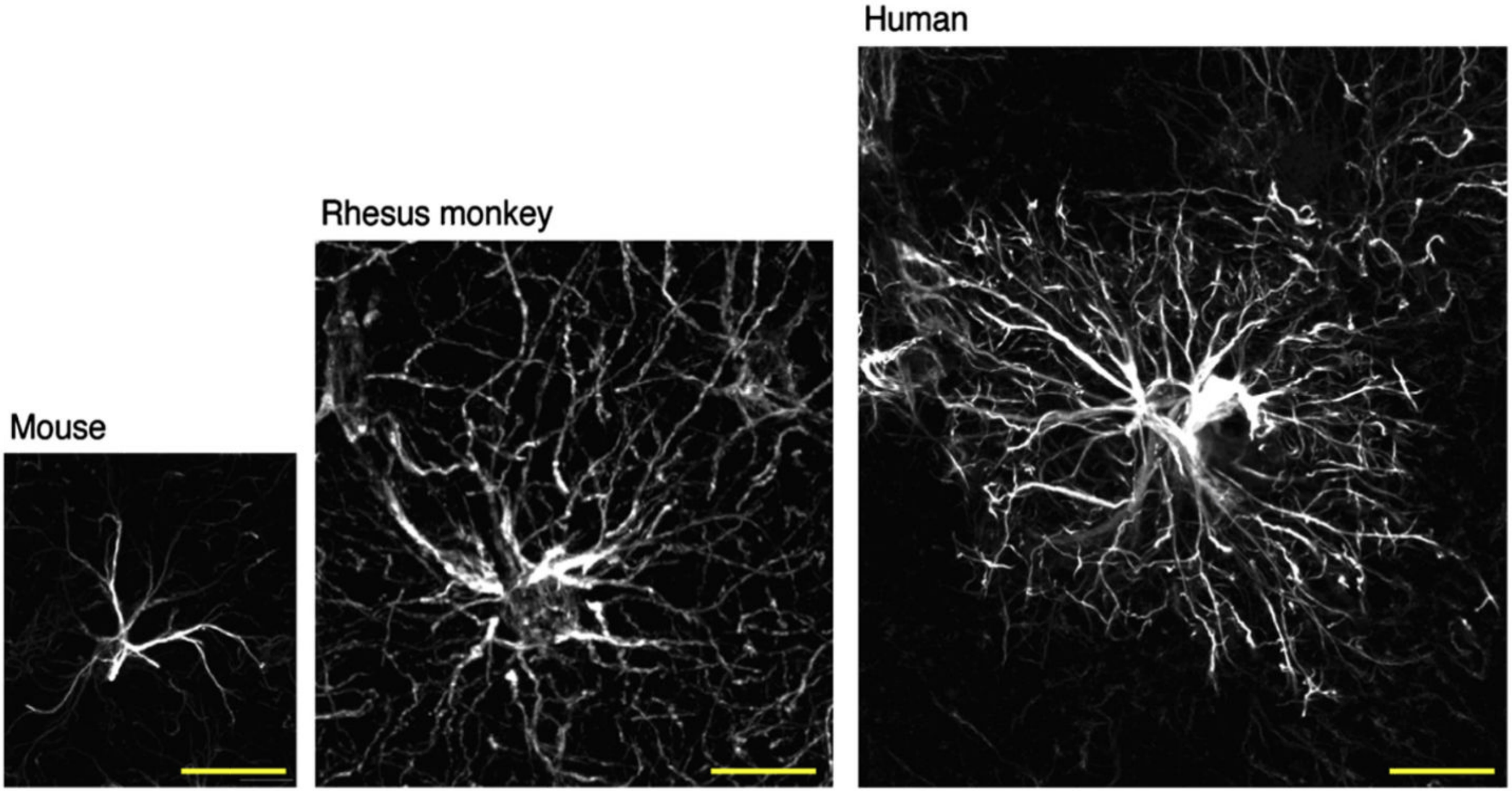
Immune to brain communication

- Tells you when you are sick.
  - Cytokines communication with the brain
  - Interleukin 1β and TNF-α both do this

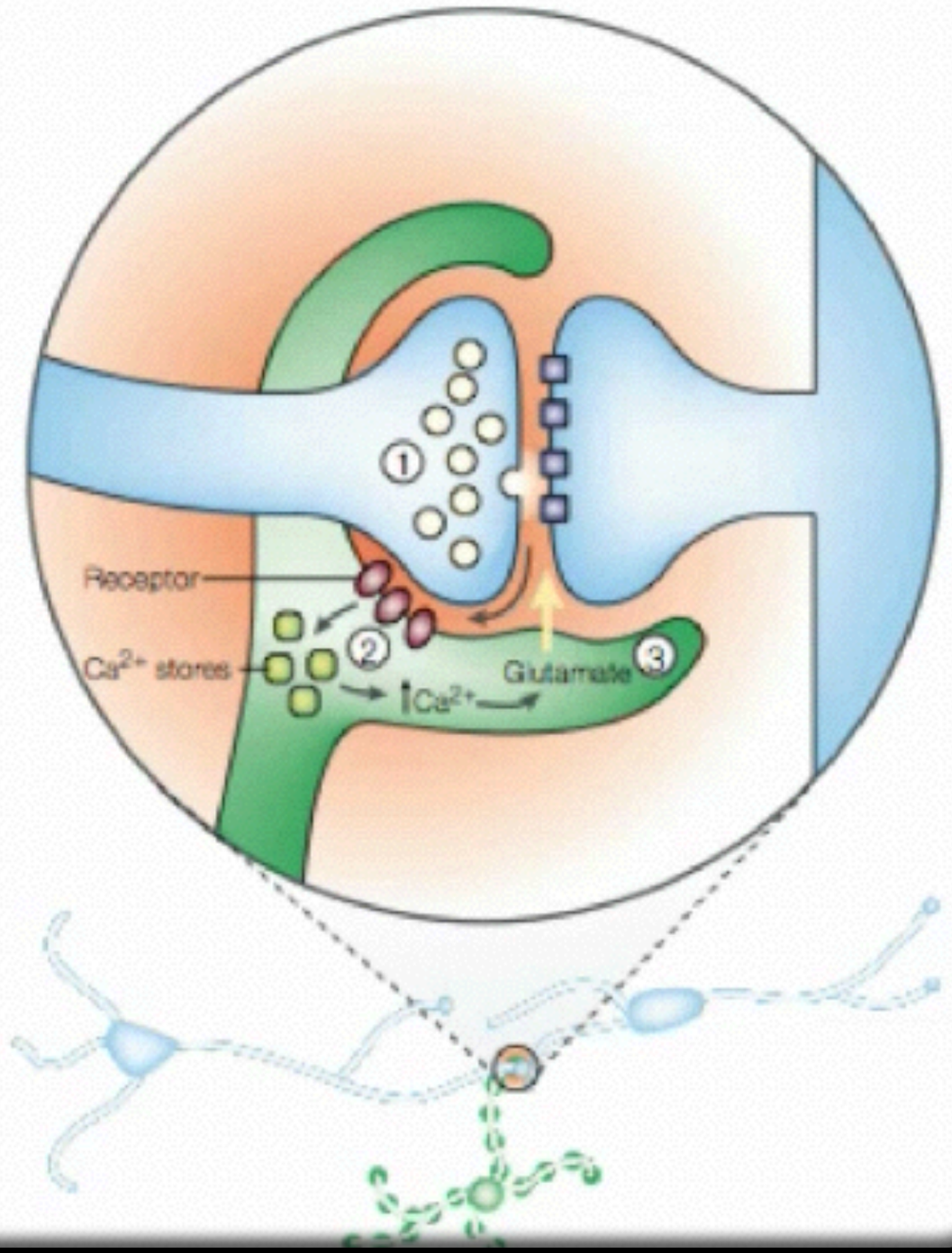
Astrocyte Functions

- Blood brain barrier
- Synaptic regulation
- Nutrient supply to neurons
- Immune signalling
- Calcium waves

Astrocytes

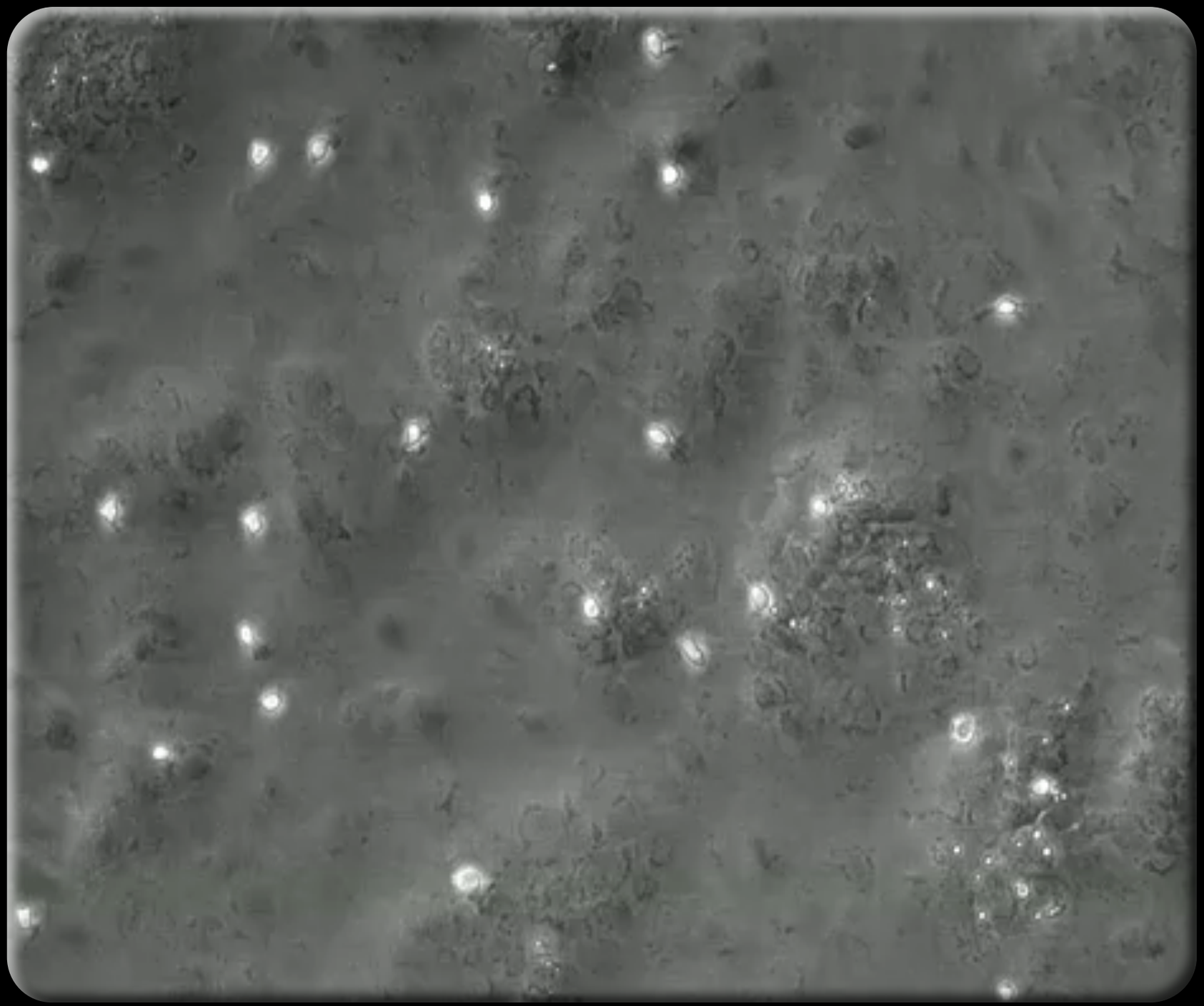


Astrocytes



- The tripartite synapse
  - Astrocytes modify the transmission of signals
- Glutamate take up by
  - GLAST
  - GLT-1

Microglia



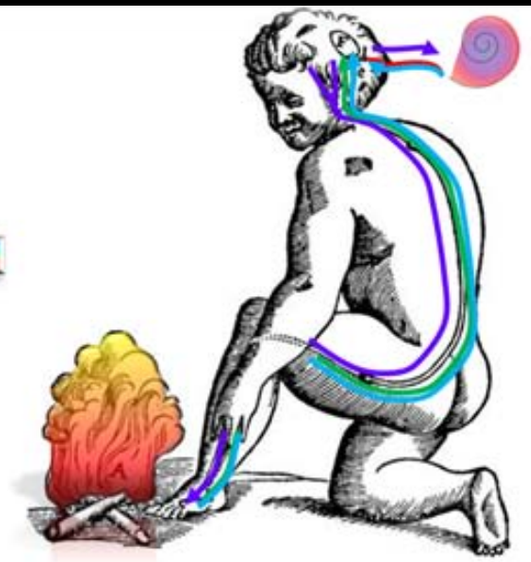
Constantly survey the brain

Touch every part of the brain 3x / hour

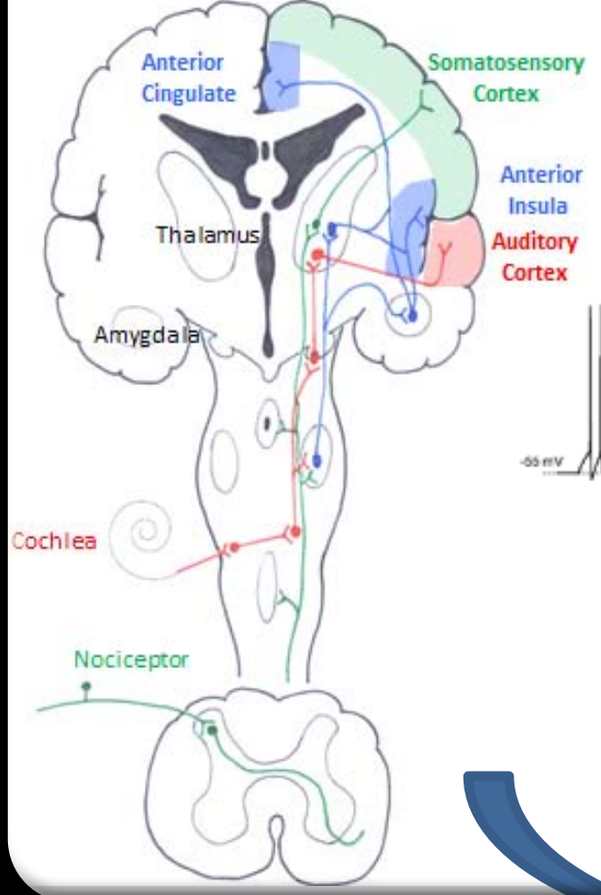
Rapidly respond to injury

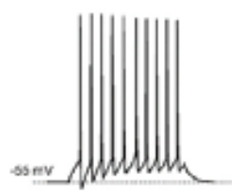
Recap

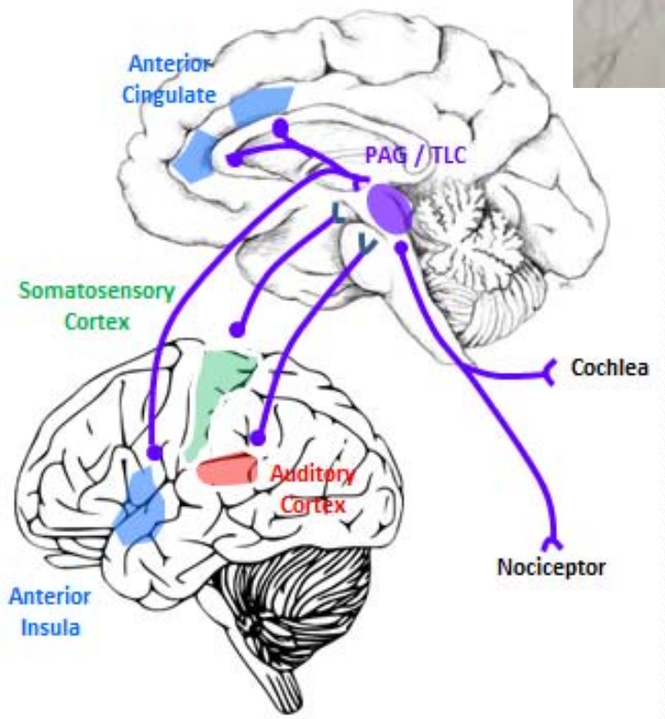
Ascending
Nociceptive
Noise-sensing

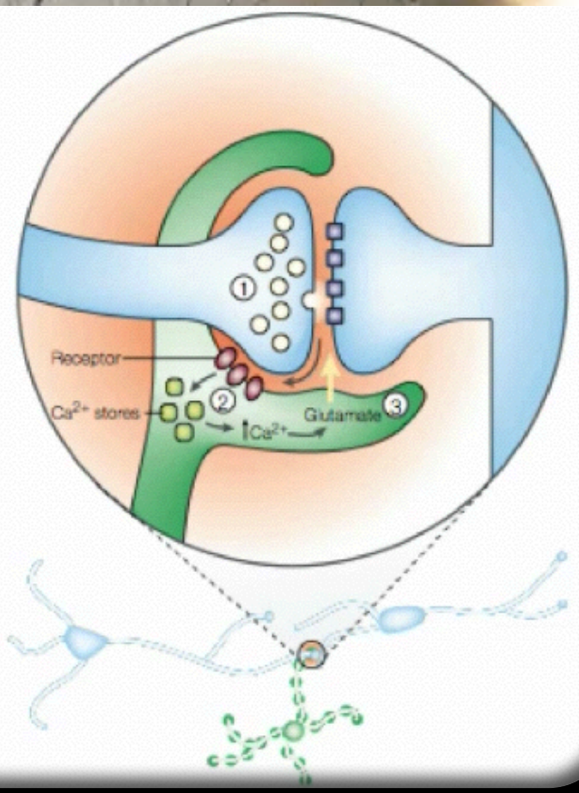


Descending
Anti-nociceptive
Noise-canceling









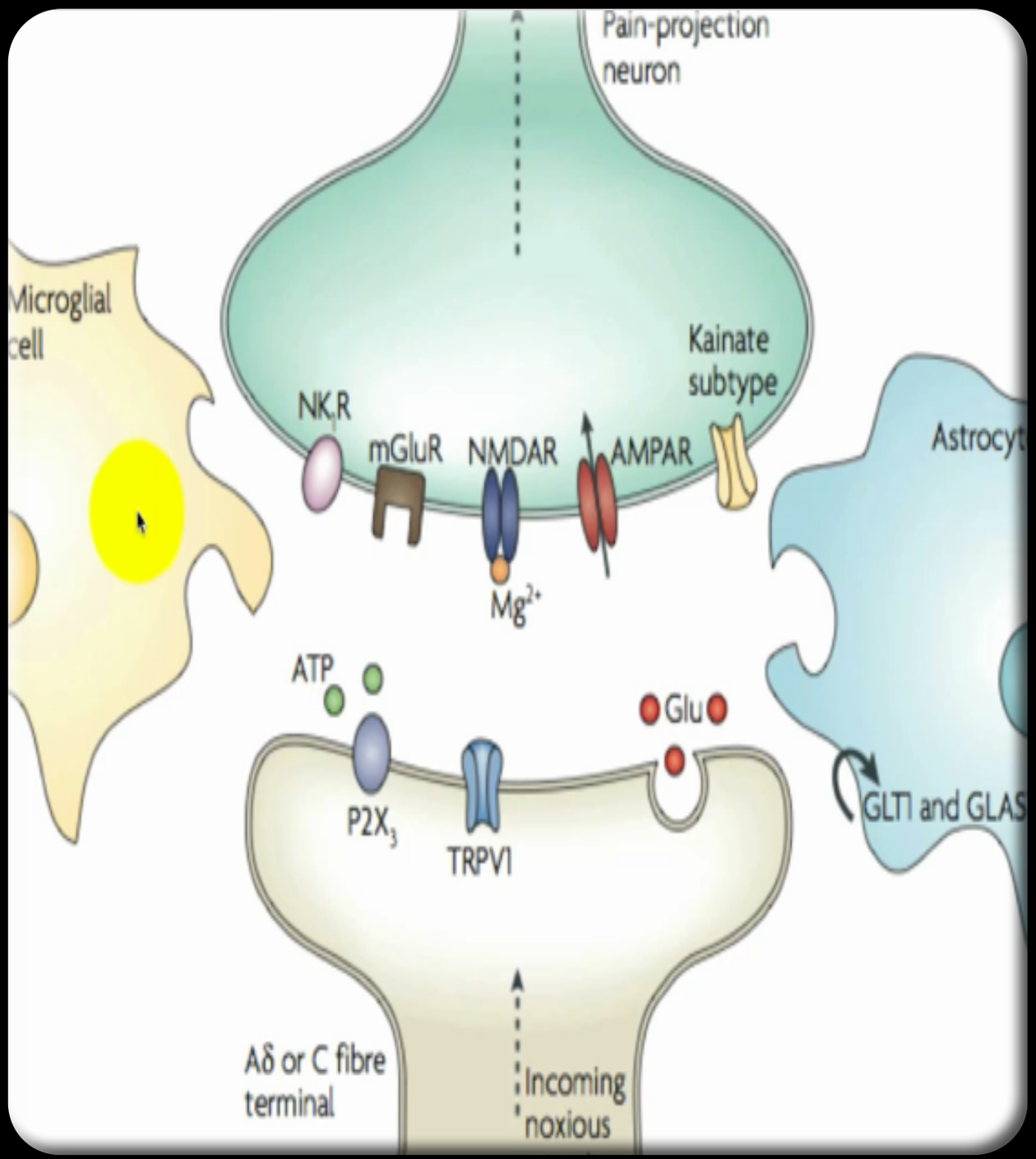
If not salient

Neuro-immunopharmacology

Complexity of pain pathways

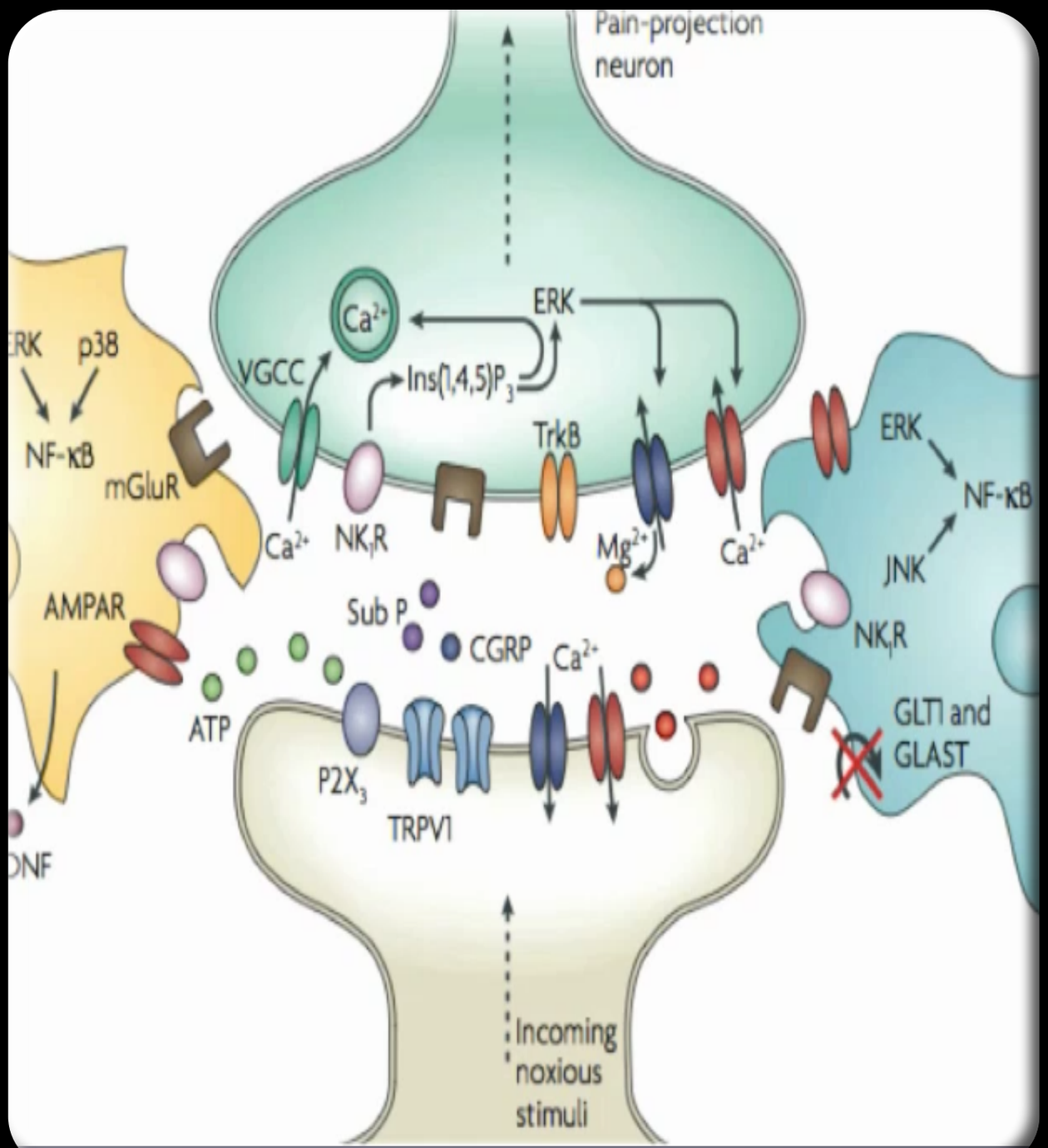
- Over 200 genes expressed with pain involving multiple pathways
  - Activation of certain gene expression with pain
- Many of these genes relate to neuroimmune activation

Neuronal Transmission



- Normally requires ongoing function of astrocytes
  - Microglia don't seem to do much until activated
- Glutamate is main synaptic transmitter

Neuronal Transmission With Pain



- Astrocytes
  - GLT/ GLAST down
- Microglia
  - Inflammatory responses
  - Retasking of Aβ fibres
- Other things with pain:
  - Presynaptic glutamate, CGRP, Substance P release
  - Post Synaptically NMDA activation via ERK

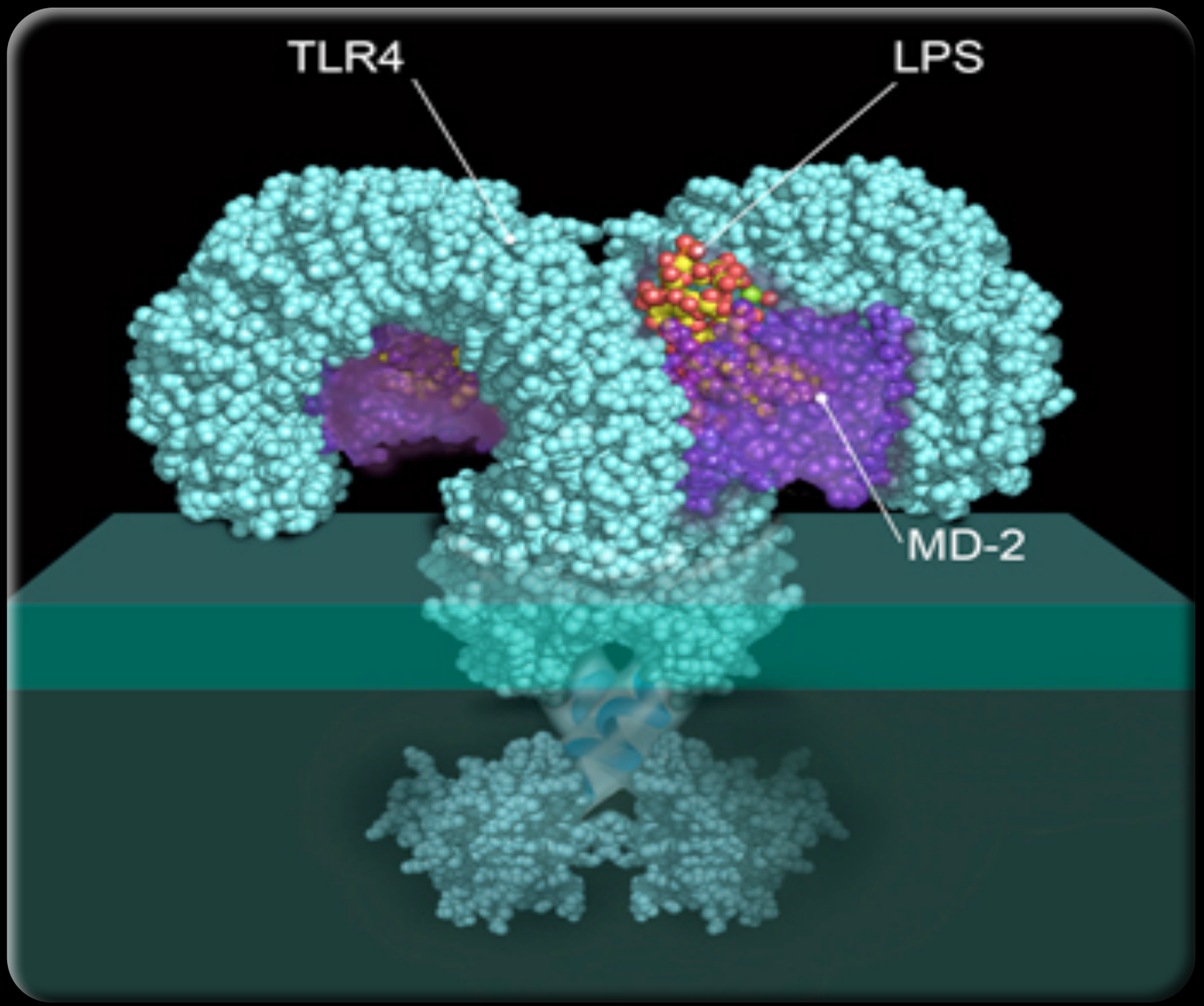
Immune activity in glia

- Two sorts of immune systems
  - Acquired immunity, immunoglobulins
  - Innate immunity, toll like receptors (TLR)
- Microglia use innate immunity signalling
  - The TLR receptor is part of the endotoxin shock response.

Toll like receptors

- Over 10 types of TLR's
  - TLR4 - endotoxin and sepsis
  - TLR2 - yeast
  - TLR 7,8,9 - viral products
- Recognise danger associated molecular patterns (DAMP's)
  - Things that are released by stressed cells
  - Eg Heat shock protiens, oxidised lipids.
  - Wallerian degeneration of neurons

TLR 4



TLR 4

Toll-like Receptor 4

LPS

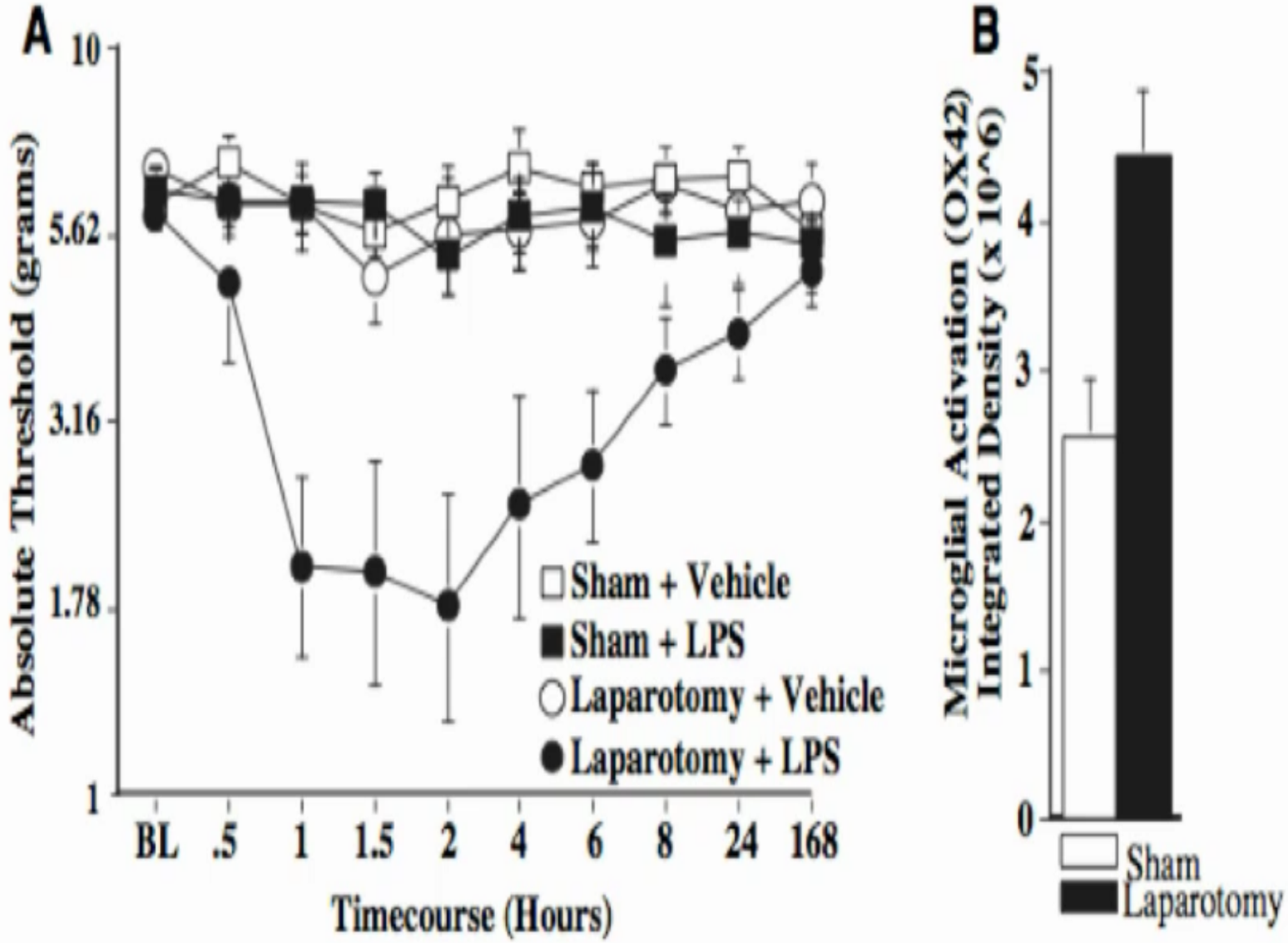
Lipopolysaccharide

Probably requires a heat shock protein cofactor as well

Synapses aren't simple

- Pain may be initiated by nociception
  - Glial activation is needed to maintain chronic pain states
- Lipopolysaccharides activate glia via TLR4

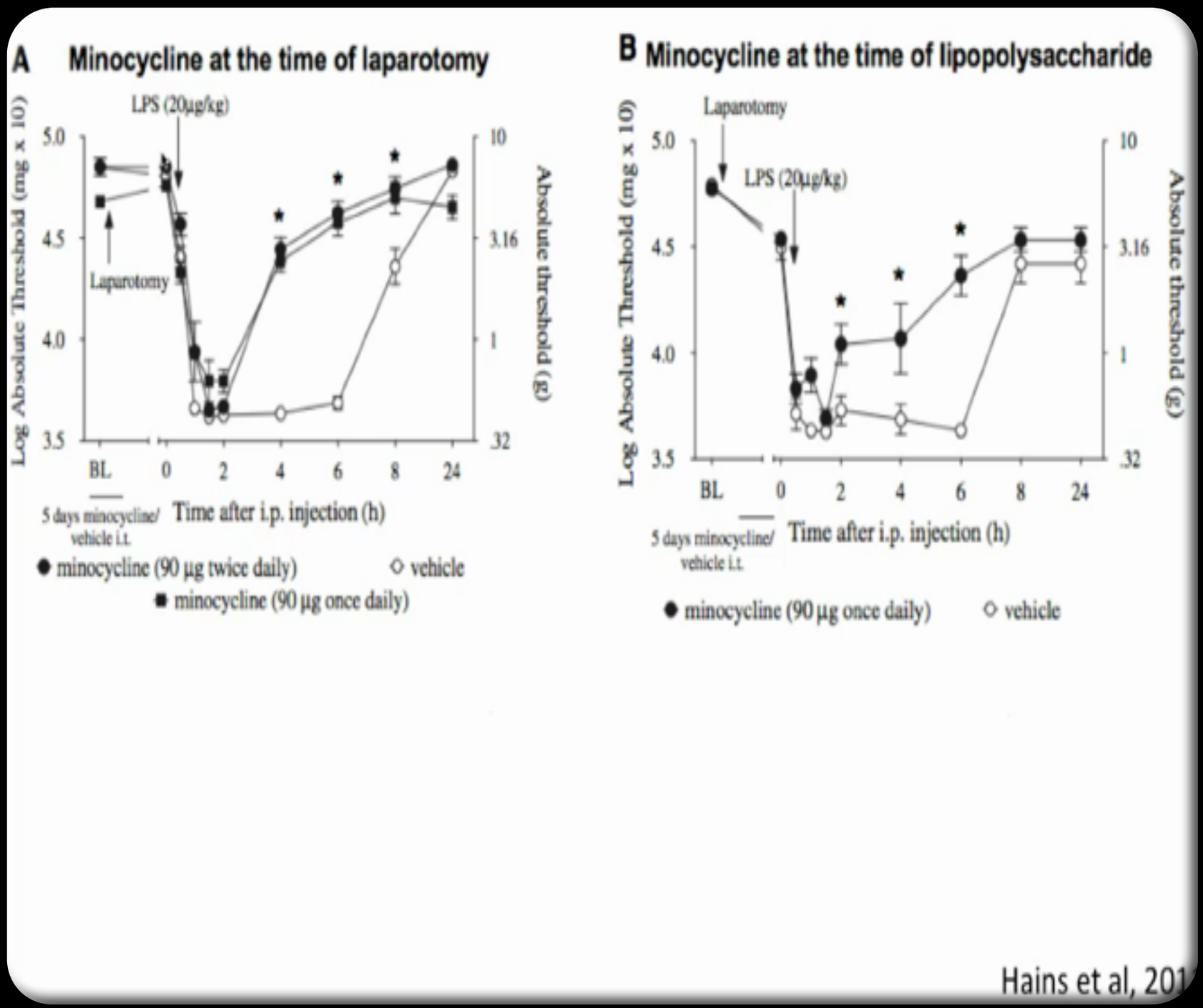
Allodynia
2-hit hypothesis



Hains et al, 2011

- To have allodynia you need
  - Nociception
  - Inflammation

Minocycline blocks this



Hains et al, 201

Minocycline blocks microglial activation

Blocking microglia blocks allodynia (in rats)

Also, TLR4 knockout mice have less pain

In experimental animals

Table 1–Pain models associated with upregulation of spinal cord microglial and/or astrocyte activation markers

Complete Freund's adjuvant, subcutaneous
Formalin, subcutaneous
Phospholipase A2, subcutaneous
Zymosan, subcutaneous
Sciatic nerve injury (chronic constriction injury)
Inferior alveolar and mental nerve transection
Partial sciatic nerve ligation
Sciatic nerve inflammation with zymosan
Sciatic nerve inflammation with HIV-1 gp120
Sciatic nerve inflammation with phospholipase A2
Spinal nerve transection
Spinal nerve root injury
Spinal cord injury
Hind paw incision
Bone cancer
HIV-1 gp120, intrathecal
Lipopolysaccharide, intrathecal
Chronic opioids; opioid withdrawal-induced hyperalgesia

Modified and updated from Ledeboer et al. (2006).

- Pretty much every pain model that produces allodynia is associated with glial activation

In experimental animials

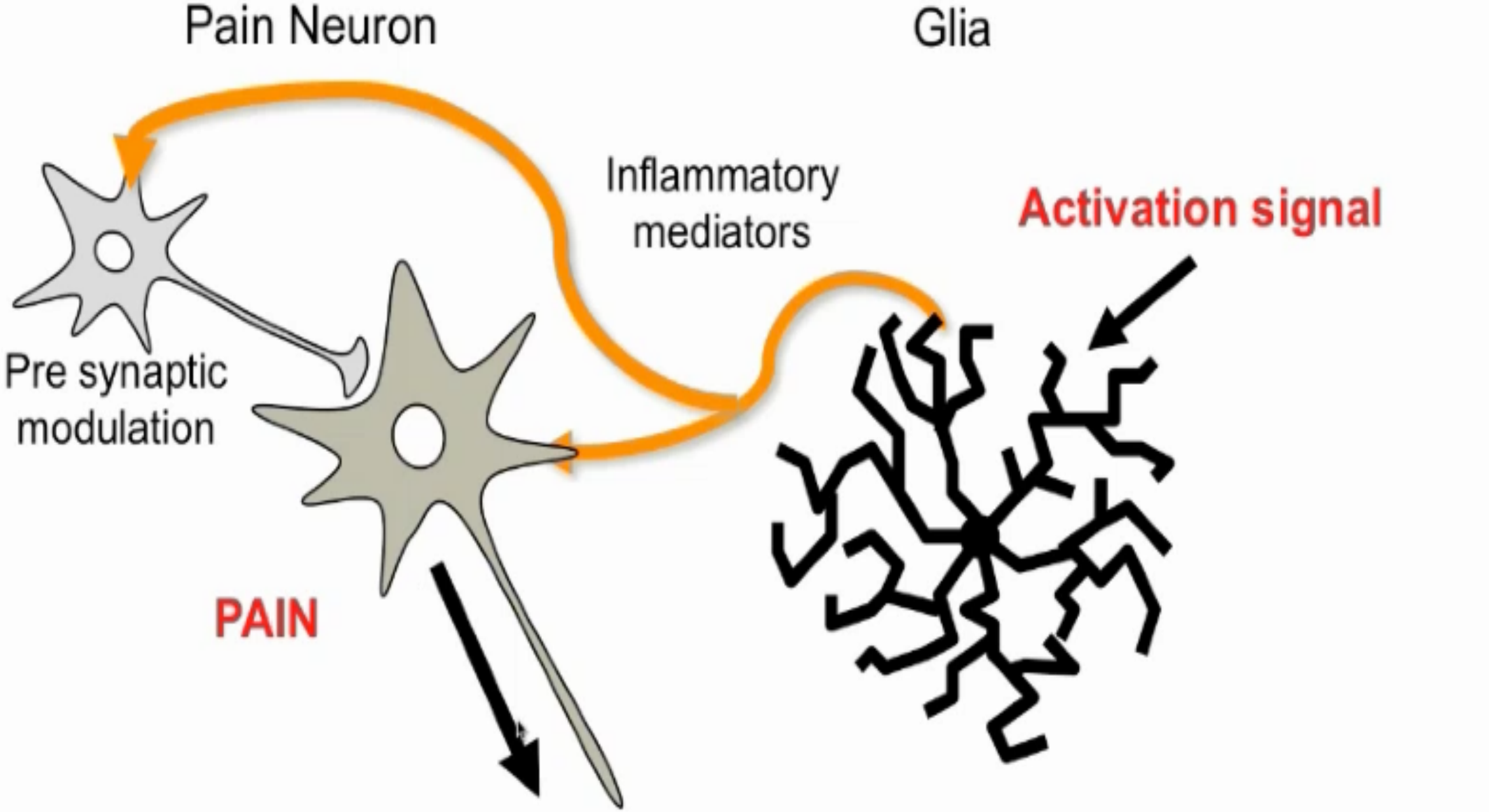
Table 2 – Pain facilitation is suppressed or reversed by inhibition of spinal glial activation or proinflammatory cytokine actions

Model	Intervention
Mustard oil, topical	Fluorocitrate
Carrageenan, subcutaneous	Minocycline, IL-1 knockout
Complete Freund's adjuvant, subcutaneous	IL-1ra, IL-1 knockout
Formalin, subcutaneous	Fluorocitrate, IL-1ra, minocycline; IL-1 knockout
Phospholipase A2, subcutaneous	Fluorocitrate, IL-1ra, sTNFR
Zymosan, subcutaneous	Fluorocitrate
Hind paw incision	Fluorocitrate
Inferior alveolar and mental nerve transection	Minocycline
Sciatic nerve injury (chronic constriction injury)	IL-1ra, IL-10; IL-1 knockout
Sciatic nerve inflammation with zymosan	Fluorocitrate, minocycline IL-1ra, sTNFR, IL-6 antibody
Sciatic nerve inflammation with phospholipase A2	IL-1ra, anti-IL-6, IL-10
Sciatic nerve tetanic stimulation	Fluorocitrate
Spinal nerve transection	Propentofylline, minocycline, IL-1ra, sTNFR, anti-IL-6,
Spinal nerve root injury	Methotrexate; IL-1 knockout
Spinal cord injury	IL-10, IL-1ra, minocycline
HIV-1 gp120, intrathecal	Fluorocitrate, IL-1ra, sTNFR, minocycline
Lipopolysaccharide, intrathecal	IL-1ra
Dynorphin, intrathecal	IL-1ra, IL-10
Fractalkine, intrathecal	Minocycline, IL-1ra, anti-IL-6

Abbreviations: IL-1ra, interleukin-1 receptor antagonist; sTNFR, soluble TNF receptor; IL-10, interleukin-10.
Modified and updated from Ledeboer et al. (2006). For complete references, see Clark et al. (2006), Hains and Waxman (2006), Honore et al. (2006a), Ledeboer et al. (2006), Obata et al. (2006), Piao et al. (2006), Watkins et al. (2005), and Xie et al. (2007b).

- Pain facilitation is inhibited by inhibitors of spinal glial activation

Neuropathic pain pathway



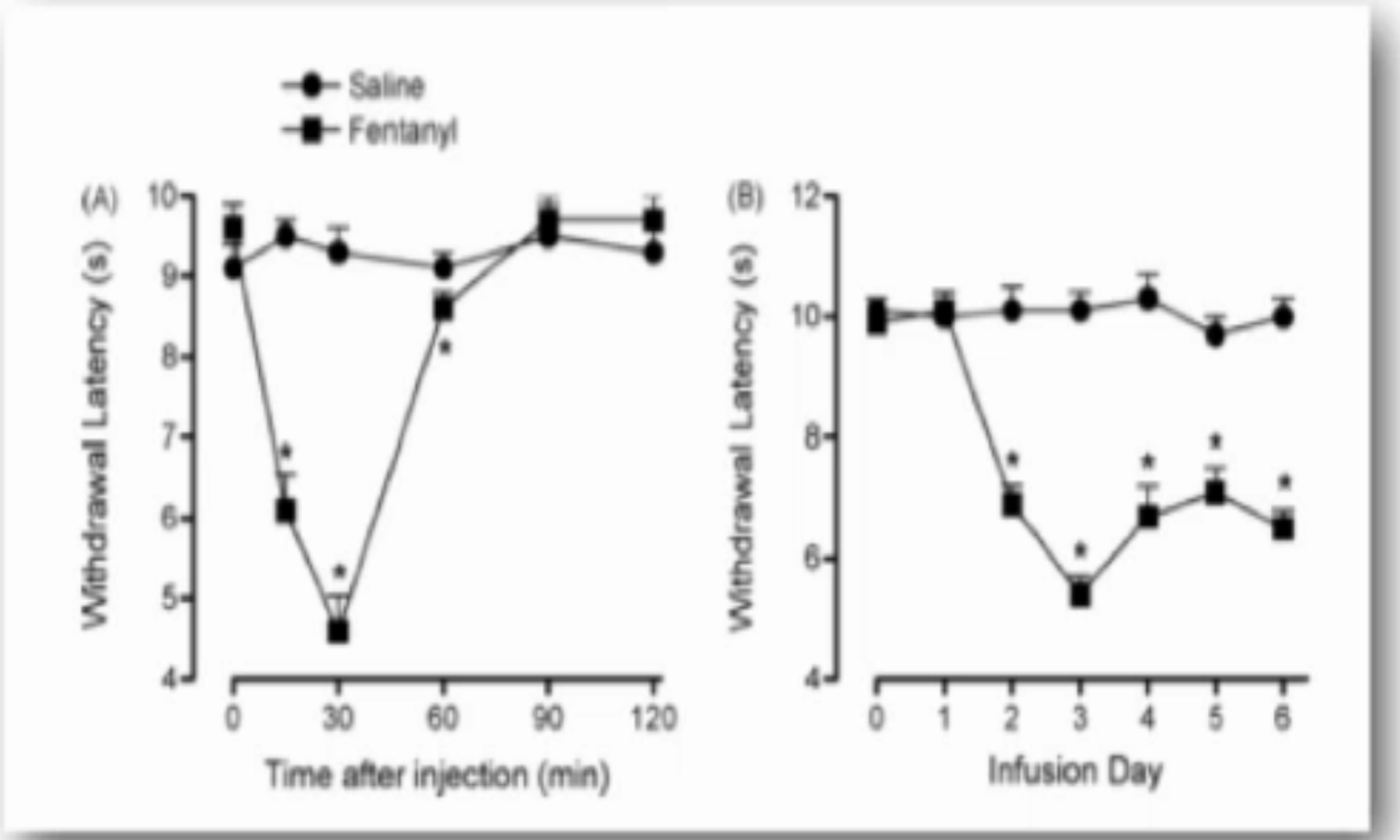
Opioids and Glia

Issues with opiates

- Tolerance
- Opioid induced hyperalgesia
- Addiction
- Don’t work well for chronic pain.
- But why?

Knockout mice

Waxman et al 2009



Triple knockout mice

No DOP/MOP/KOP

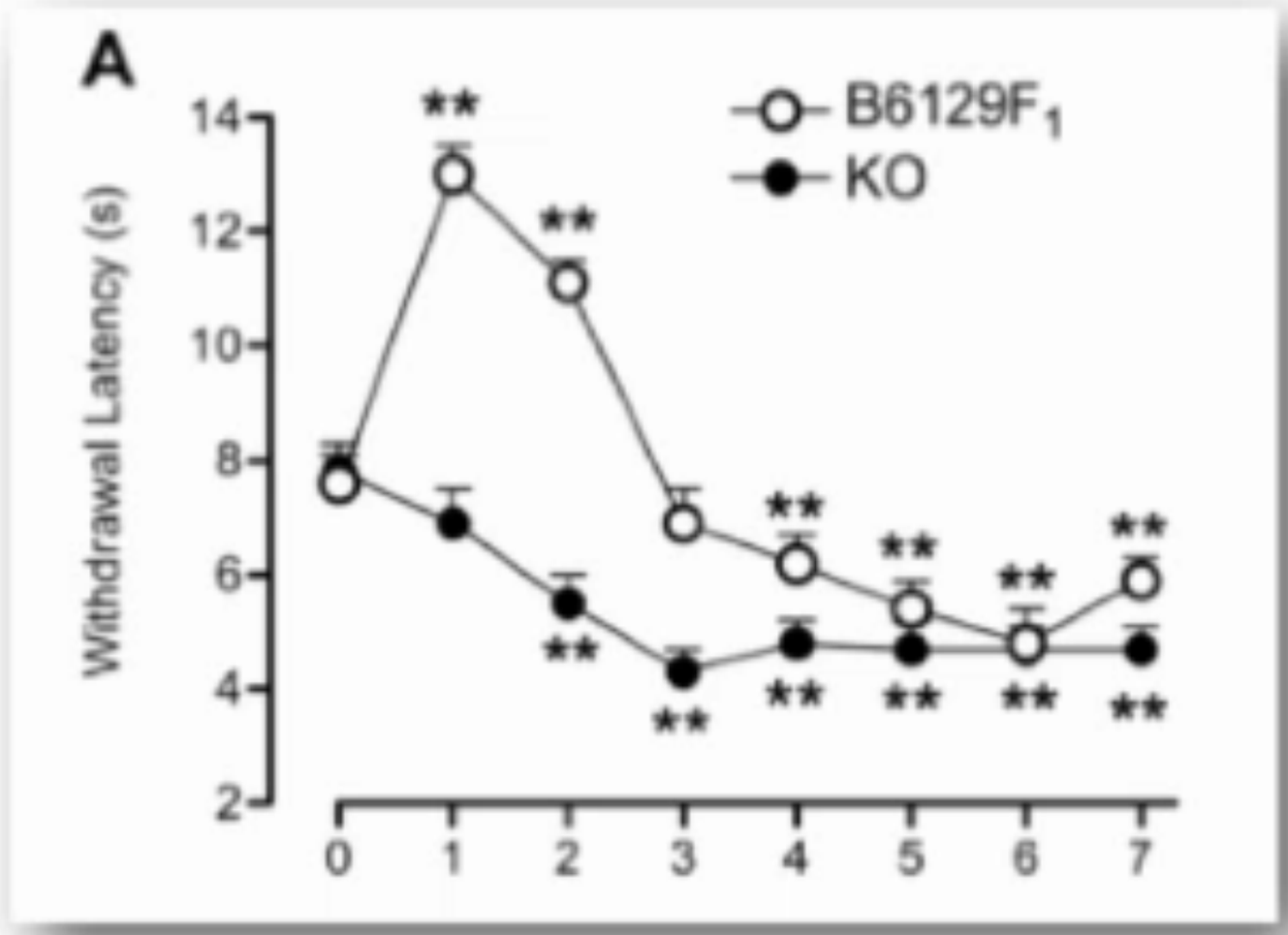
In these mice:

Fentanyl produces hyperalgesia immediately

Produces allodynia with sustained infusions

Compare with normals

Juni et al 2007



Similar with oxymorphone in knockout mice (KO)

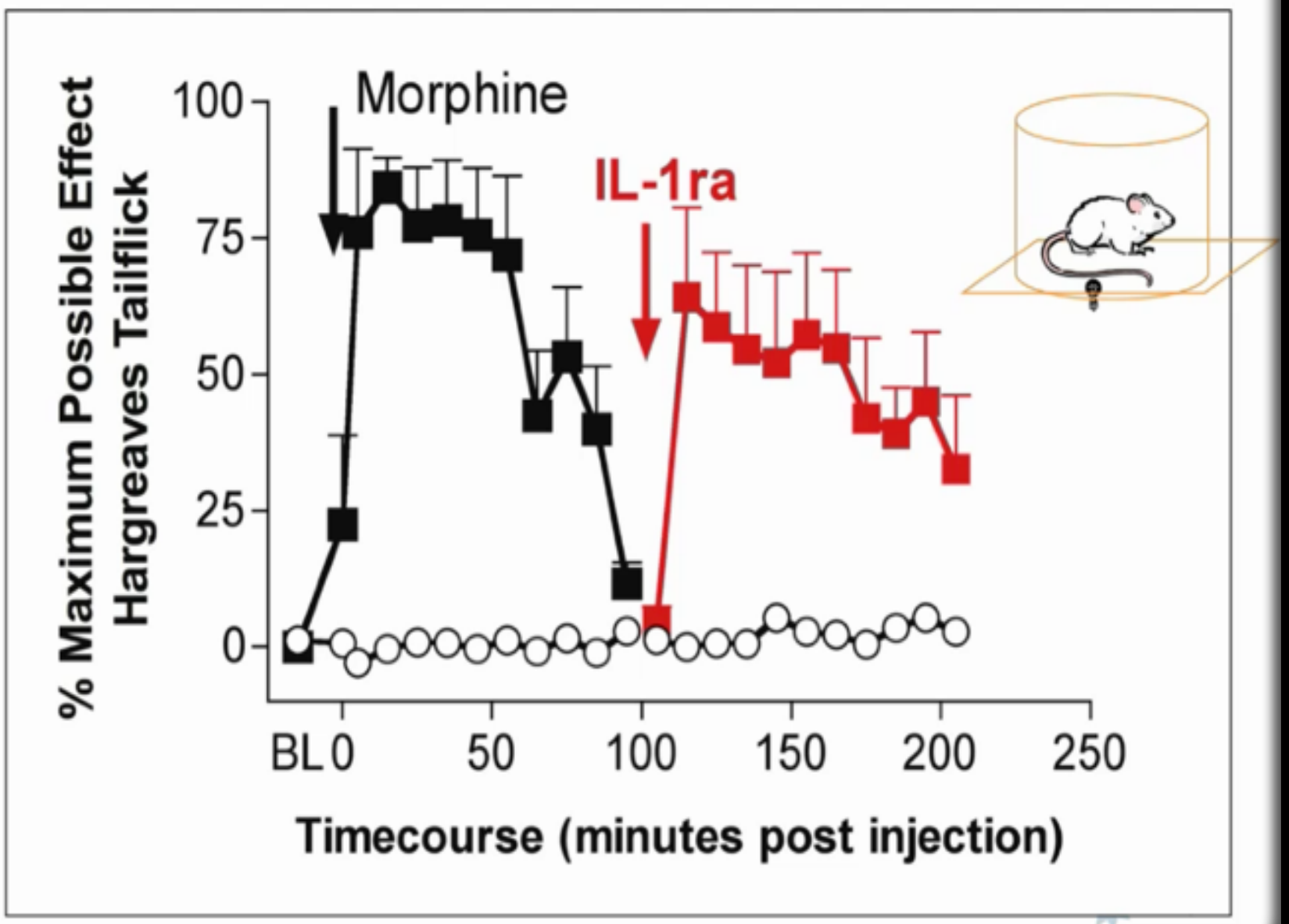
But the endpoint after a few days is identical in wild mice

Net effect of this

- Opioids antagonise their own actions

- Initial response is still analgesia
- Subsequent response is allodynia

Blocking IL1 restores analgesia

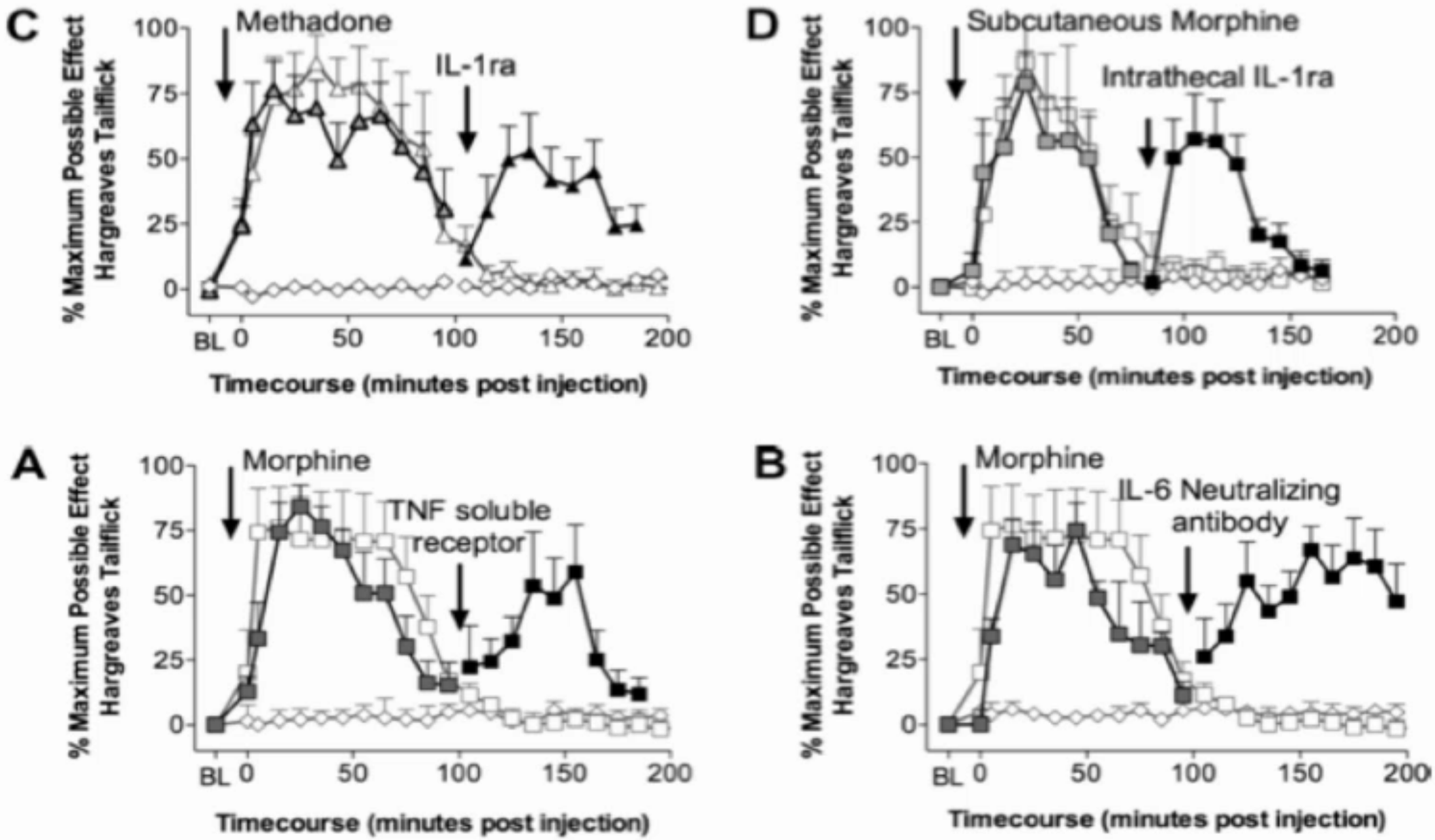


Hutchinson et al 2008

Morphine antagonises its own action

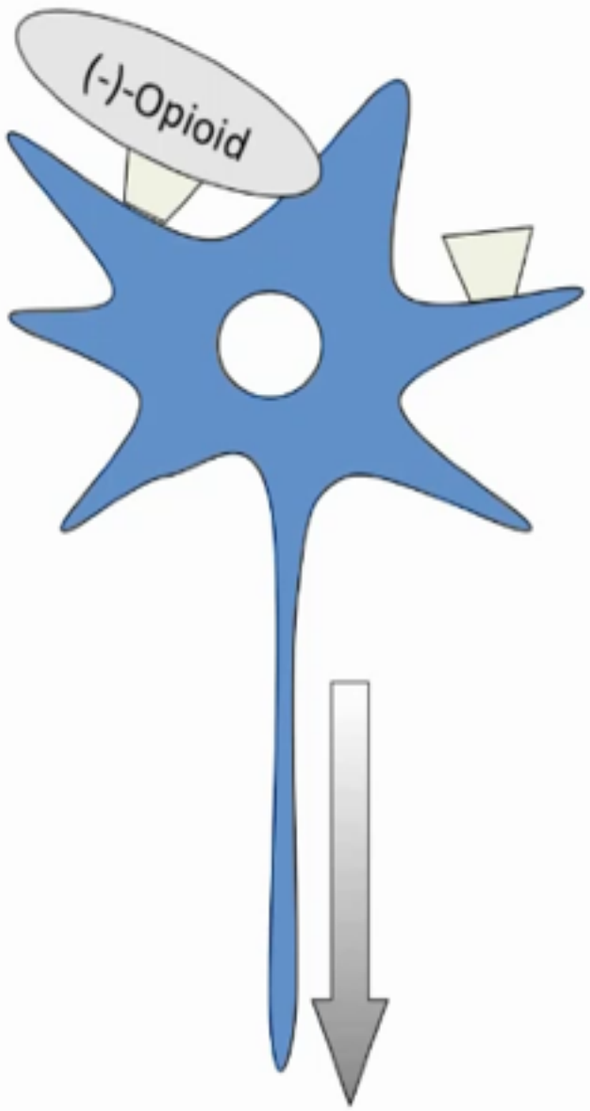
The mechanism for antagonism isn't via opiate receptors

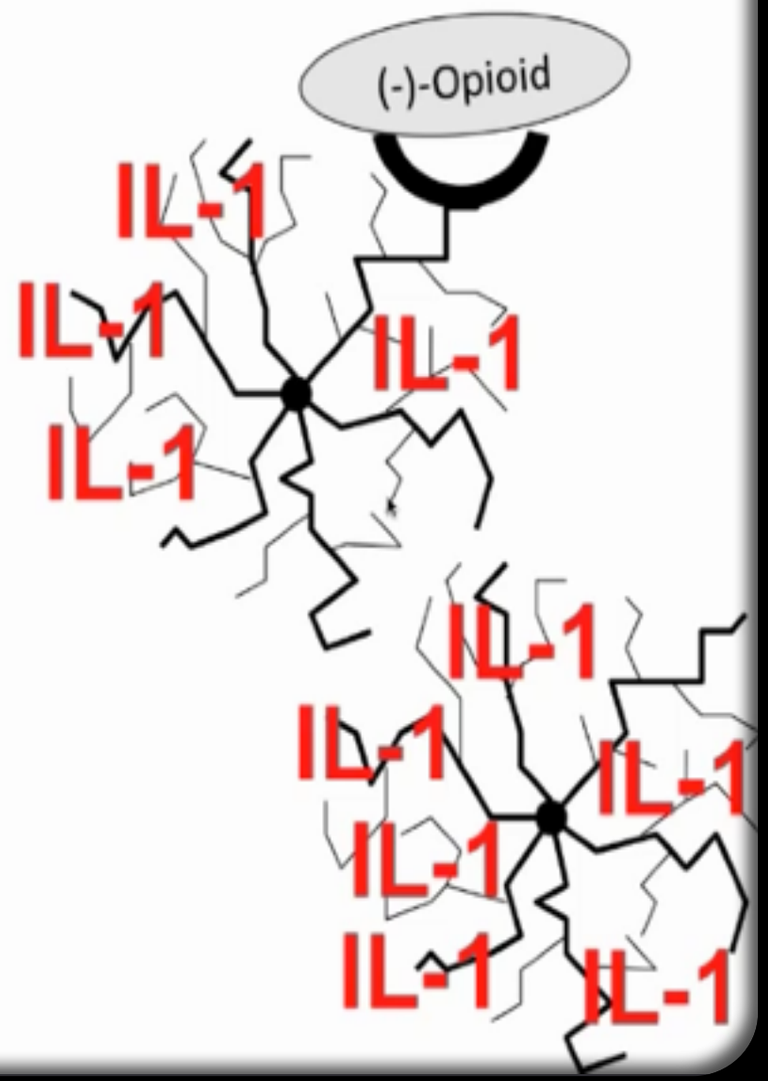
Its not just morphine and IL-1



Hutchinson et al 2008

Dual effect



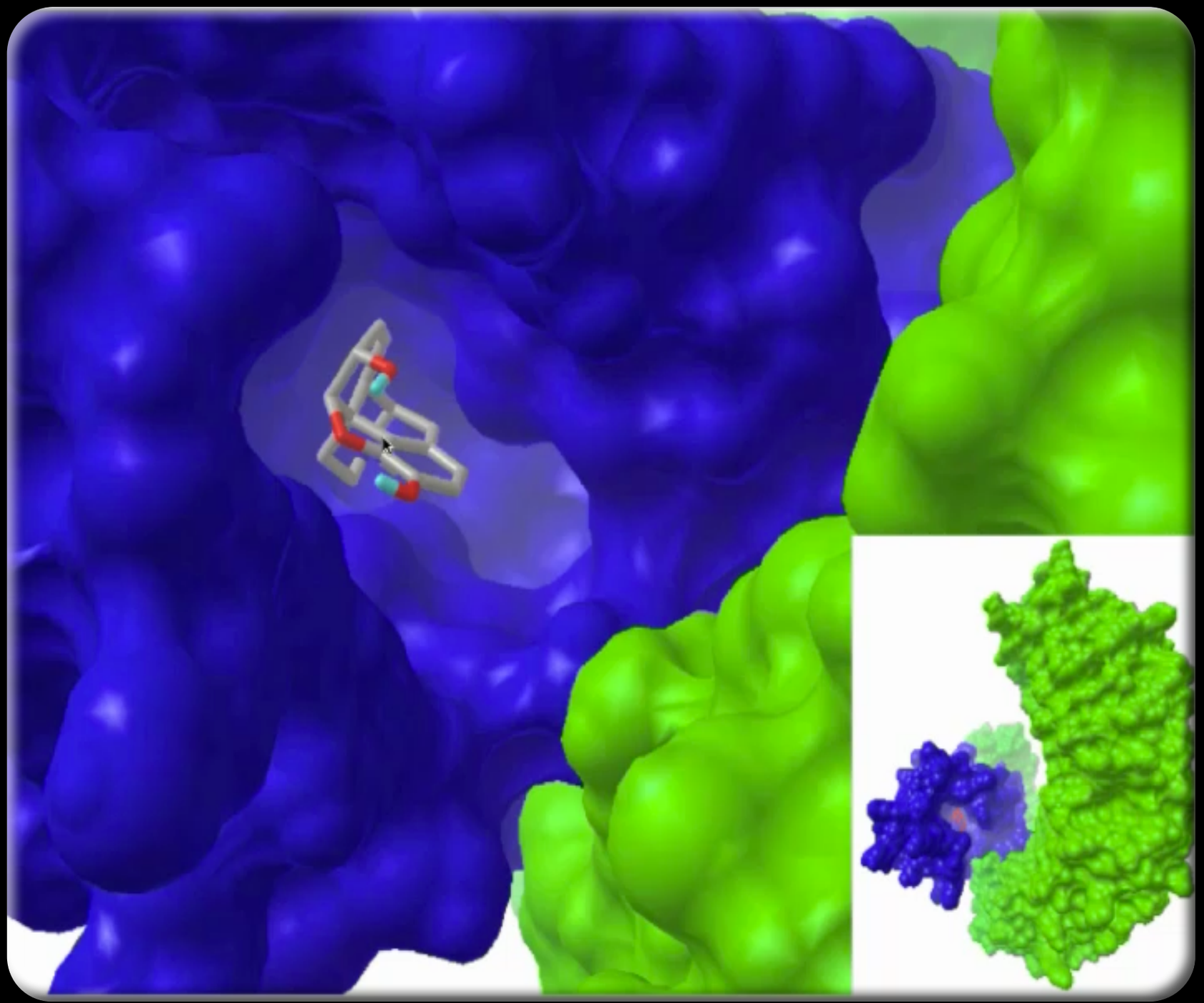


At the same time that opioids are acting on neurons, they are acting on glial cells.

But how do opiates do this

- Appears to be related to the toll like receptors
- Even more interesting, this can be blocked

Morphine and TLR-4



Morphine binds the same site as LPS in the MD2 accessory protein to TLR-4

Chronic Pain Management

- Multipronged treatment strategy
  - Biological
    - Pharmacological
    - Physical
    - Interventional
  - Psychological
  - Social

Pharmacological Therapies

Gabapentinoids

- Pregabalin, Gabapentin
  - Binds to voltage dependent calcium channel
    - Decreases Glutamate, NorAdr, Substance P and Calcitonin
- Significant side effects
  - Dizziness and drowsiness
  - Weight gain

Tricyclic Antidepressants

- Amitriptyline, Nortriptyline
  - Inhibit Serotonin and Noradrenaline reuptake
  - Some inhibition of Serotonin, Histamine, muscarinic, alpha adrenergic and dopaminergic receptors
- Significant side effects
  - Anticholinergic effects most common

Tramadol

- Combined μ, Serotonin and Nor adrenergic agnonist
  - Effective against acute and chronic pain
- Low addition potential
- Side effects common (esp N+V, sweating)

Tapendatol

- Tapendatol (μ agonist and NorAdr reuptake inhibition)
  - Like tramadol without sertonergic side effects
  - Still a schedule 8 drug
  - Currently only in slow release form

Mu (μ, MOR) agonists

- All have very little benefit in chronic pain
  - Almost no benefit versus placebo
- Significant problems
  - Tolerance, dependence
  - Addiction
  - Opioid induced hyperalgesia

Drug	Condition	NNT	NNH
Opioids	Neuropathic Pain	2.5	4.2-8.3
Tramadol	Neuropathic Pain Post surgical Pain	3.4 2.4-4.8	8.3
Tricyclics	Neuropathic Pain	3.6	6 (minor) 28 (major)
Gabapentinoids	Central Neuropathic pain Diabetic Neuropathy Post Herpetic Neuralgia Fibromyalgia	5 2.9-5 3.9 13-22	3.7
Venlafaxime **Duloxitine**	Neuropathic Pain	3.1 6-8	9.6 (minor) 16.2 (major)
Paracetamol	Chronic Arthritic Pain	4-5	12 (GI s/e)

Clinical Principles

- Acute inflammatory / Nociceptive pain
  - Paracetamol & NSAID's for inflammatory pain
  - Tramadol and Opiates for more severe pain
- Chronic / Neuropathic pain
  - Gabapentinoids, SNRI's and TCA's
  - Tramadol
  - Avoid opioids if possible, Buphrenorphine best

Summary

Pain

Definitions
Physiology
Pharmacology

Chronic Pain

Pathophysiology
Pharmacology